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(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND POLYGLYCOLIZED GLYCERIDES

(57) Abstract

A pharmaceutical composition is provided for treating hyperlipidemia or hypercholesterolemia or both in a mammal, which contains an effective amount of each of fenofibrate and an excipient containing one or more polyglycolyzed glycerides.

PHARMACEUTICAL COMPOSITION CONTAINING FENOFIBRATE AND POLYGLYCOLIZED GLYCERIDES

BACKGROUND OF THE INVENTION

Field of the Invention:

The present invention relates to a pharmaceutical dosage form of fenofibrate having enhanced bioavailability, as well as to an advantageous process for making the same.

Description of the Background:

Fenofibrate or p-(4-chlorobenzoyl)-phenoxy isobutyrate isopropyl ester is useful for the treatment of adult patients with very high elevations of serum triglyceride levels and/or cholesterol levels. The usual daily dosage is 300 mg which is administered in two or three doses. Fenofibrate is absorbed as fenofibric acid which is responsible for the pharmacological activity. Fenofibric acid resulting from the hydrolysis of fenofibrate is extensively bound to plasma albumin. The plasma half-life is about 20 hours. Fenofibric acid is excreted predominantly in the urine, mainly as the glucuronide conjugate, but also as a reduced form of fenofibric acid and its glucuronides.

Fenofibrate, is presently available in a pharmaceutical dosage form consisting of hard gelatin capsules containing fenofibrate, lactose starch and magnesium stearate. After oral administration, during a meal, about 60% of the dose of this conventional form is

effectively absorbed and found in the blood as fenofibric acid, the main metabolite responsible for pharmacological activity. (Strolin & Al, Act Pharmacal. Toxicol. 1986; 59 (Suppl. 5); 167).

The first attempt to improve the bioavailability of fenofibrate was performed by Ben-Armor and Al, by solubilizing the fenofibrate in dimethyl isosorbide, a nonaqueous solvent with a miscible wetting agent (Labrafil M 1944CS) with HLB of between 3-4. In order to use the product in capsules, colloidal silicon oxide was added to increase the viscosity. The liquid so obtained was placed in hard gelatin capsules which, to be leak proof, were sealed. In vivo studies with this formulation indicate that there was no statistically significant difference in bioavailability between this liquid formulation and the conventional form when the product was given with food.

European Patent Application 0330532 discloses a fenofibrate composition wherein the fenofibrate powder is co-micronized with a solid wetting agent. Sodium lauryl sulfate is described as the solid wetting agent of choice. The co-micronized powder so obtained is mixed with capsule filling excipient such as lactose, starch, polyvinyl pyrollidone and magnesium stearate. A formulation of this composition is actually available on the French market under the trade name Lypantyl 200 M®. A study comparing this formulation (Lypantyl 200 M®) to the conventional form

was undertaken and a statistically significant increase in bioavailability was indicated for the former. In particular, it was found that 67 mg of the new form gives the same amount absorbed as does 100 mg of the conventional form. (J.L. Suichard & Al Cun Therapeutic Research Vol. 54, NS, Nov. 1993).

Unfortunately, co-micronization of the active drug fenofibrate with the wetting agent sodium lauryl sulfate, although necessary, is a time consuming and costly operation. Further, an inherent drawback of micronization is that the material obtained must comply with very stringent particle size specifications.

Moreover, the filling of hard gelatin capsules with a micronized powder is a difficult operation, particularly if weight variation homogeneity is considered.

Hence, a need exists for a fenofibrate formulation that avoids the use of co-micronization, while providing a bioavailability comparable to that afforded by the conventional fenofibrate formulation which uses co-micronization.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a fenofibrate formulation not requiring use of co-micronization which, nevertheless, exhibits a

bioavailability comparable to formulations of fenofibrate which do.

It is also an object of the present invention to provide a solid, oral dosage form of a fenofibrate formulation that can be prepared by melting the excipients in which the fenofibrate is soluble and, therefore, does not require any particle size specification.

The above objects and others are provided by a pharmaceutical composition for treating hyperlipidemia in and/or hypercholeslerolemia a mammal, which contains an effective amount of each of fenofibrate and an excipient containing one or more polyglycolized glycerides.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a pharmaceutical formulation for treating hyperlipidemia and/or hypercholesterolemia in a mammal, which contains an effective amount of each of a fenofibrate composition and an excipient which contains one or more polyglycolyzed glycerides, the polyglycolyzed glycerides preferably having an HLB value of at least about 10.

The prevent invention is also particularly advantageous for the production of oral solid dosage forms which can be prepared by melting the excipients in which the fenofibrate is soluble, whereby particle size specifications are not required.

The present invention also relates to the addition of a suspension stabilizer to the molten solution of fenofibrate-polyglycolyzed glycerides. The suspension stabilizer avoids the formation of fenofibrate crystals during the cooling of the filled hard gelatin capsules. Suitable suspension stabilizers which may be used are, for example, cellulose derivatives, such as hydroxypropylcellulose, hydroxypropylmethyl cellulose, methyl cellulose, and hydroxyethylcellulose, povidone, poloxamers, α, Ω-hydroxy-poly(oxyethylene) poly(oxypropylene)-poly(oxyethylene)bloc polymers. Other suspension stabilizers equivalent to these stabiliers may, of course, also be used.

The present invention is also particularly advantageous for the production of a pharmaceutical composition in that the hot, homogeneous fenofibrate solution is filled in hard gelatin capsules. This filling process permits the obtention of very precise fenofibrate amounts in each capsule.

The present invention is particularly advantageous as well for the production of the present pharmaceutical composition in that the process for manufacturing the composition requires very few steps such as melting, mixing and filling. This renders the present manufacturing process extremely cost effective when compared to one using co-micronization of powders.

Polyglycolyzed glycerides which may be used in the present invention are generally mixtures of known monoesters, diesters and triesters of glycerols and known monoesters and diesters of polyethylene glycols with a mean relative molecular mass between about 200 and 6000. They may be obtained by partial transesterification of triglycerides with polyethylene glycol or by esterification of glycerol and polyethylene glycol with fatty acids using known reactions. Preferably, the fatty acid component contains 8-22 carbon atoms, particularly 10-18 carbon atoms. Examples of natural vegetable oils which may be used include palm kernel oil and palm oil. However, these are only examples. The polyol suitably has a molecular weight in the range of about 200-6000 and preferably contains polyethylene glycol, although other polyols may be employed, such as polyglycerols or sorbitol. They are available on the market under the trade name Gelucire®.

As noted above, the HLB of the polyglycolized glycerides is preferably at least about 10, and more preferably between about 12 and 15. The melting point of the polyglycolized glycerides may be between about 18°C and 60°C. However, it is especially desirable to use polyglycolized glycerides having a melting point above 30°C, and preferably above 35°C, since there is no need for sealing the capsule, to assure the leak proofness thereof, when such excipients are used.

Further, two or more polyglycolized glycerides may be mixed in order to adjust both the HLB value and the melting point to a desired value. The HLB value and melting point of the composition may further be adjusted with the addition of components such as polyethylene glycols, polyoxyethylene glycols fatty acid esters, and fatty acid alcohols. In view of the present specification, it is well within the skill of the artisan to mix the polyglycolized glycerides to obtain desired HLB values and melting points.

It has also been discovered that the present composition affords an increased bioavailability of the fenofibrate as compared to conventional formulations.

Although the present inventors do not wish to be bound by any particular theories, one plausible mechanism of operation for the present invention is that upon cooling, the melted mixture of hot fenofibrate-polyglycolized glycerides maintains the fenofibrate in liquid form. When absorbed in the gastrointestinal tract of a patient, the gastrointestinal fluids are able to dissolve the fenofibrate due to the HLB value of the excipient mixture, whereby fenofibrate is readily absorbed.

Generally, the composition of the present invention contains from about 5% to 95% by weight of fenofibrate and from about 95% to 5% by weight of excipient including one or more polyglycolized glycerides. It is preferred, however, if the present composition contains from about 20%

to 80% by weight of fenofibrate and from about 80% to 20% by weight of excipient. It is even more preferred, however, if the present composition contains from about 30% to 70% by weight of fenofibrate and from about 70% to 30% by weight of excipient.

In a particularly preferred composition, generally about 45% to 55% by weight of fenofibrate is used and about 55% to 45% by weight of excipient containing the one or more polyglycolyzed glycerides is used.

Generally, the method of the present invention entails adding one or more excipients, including the one or more polyglycolyzed glycerides to containing means and then heating the excipients until all components are melted. Then, fenofibrate is added slowly with continuous stirring until all fenofibrate added is dissolved. Stirring is then continued for about 10 minutes to about 1 hour, and preferably for about 15 minutes to about 30 minutes. Then, containing means for the pharmaceutical composition, such as hard gelatin capsules, are filled with the composition using a liquid filing capsule machine having dosing pumps which are heated to the same temperature as the temperature of the molten pharmaceutical composition. Generally, this temperature is about 55°C to about 95°C, more typically in the range of about 80°C to 90°C. Upon cooling to ambient temperature, the capsules are packed in bottles. When

capsules of size 3 are used, each capsule so prepared contains 67 mg of fenofibrate.

It is advantageous, however, to use the following protocol. To about 3 parts by weight polyglycolized glyceride excipient having a melting point of 44°C and an HLB value of 14 molten at 80°C, is added about 2 parts by weight of fenofibrate and about 1 part by weight of hydroxypropyl cellulose. After maintaining the solution under agitation for about 20 additional minutes, hard gelatin capsules are filled therewith.

The present invention will now be further described by reference to certain examples which are provided solely for purposes of illustration and are not intended to be limitative.

EXAMPLE 1

Fenofibrate	6.7 kg
Gelucire® 44/14	5.0 kg
Polyoxamer 407	5.0 kg
	16.7 kg

In a stainless steel container, were introduced 5 kg of Gelucire® 44/14 and 5 kg of Poloxamer 407, which were then heated at 85°C until all components are molten. 6.7 kg of fenofibrate was added slowly while continuously stirring the mixture. When all of the fenofibrate was dissolved agitation was maintained for about twenty

minutes. Using a liquid filing capsule machine with dosing pumps heated at 85°C, capsules of size 3 was filled with 167 mg of solution. Upon cooling at room temperature the capsules were packaged in bottles. Each capsule so prepared contained 67 mg of fenofibrate.

PHARMACOKINETICAL STUDY

The composition of Example 1 was compared to conventional form in a pharmacokinetical study with 15 healthy subjects. Each subject received 3 capsules of composition of Example 1 (201 mg of fenofibrate) or 3 capsules of Lypantyl 100® (300 mg of the conventional form). The sessions were separated by a wash out period of 7 days. The medications were taken after a high-fat breakfast. Blood samples were obtained before and at different times up to 72 hours after administration. The plasma concentration of fenofibric acid was determined in all available samples using a conventional HPLC method.

Plasma Fenofibric Acid Concentration (mg.ℓ vs. time (h) After Administration at 3 Capsules of Example 1 (Total amount of Fenofibrate administered: 201 mg)

Post-dose time (h)	1	2	3	4	5	6	8	9	10	11	12	13	14	15	16	Mean*	SD
0	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	0	-
1	BLOQ	BLOQ	0.42	BLOQ	0.52	0.81	0.29	BLOQ	0.32	BLOQ	BLOQ	BLOQ	BLOQ	0.81	BLOQ	0.21	0.30
2	0.36	0.34	3.87	4.31	5.10	6.00	4.66	6.46	2.56	BLOQ	0.99	1.09	3.84	3.03	0.75	2.89	2.19
3	3.31	1.06	7.52	8.12	12.80	7.68	7.50	7.27	6.55	2.51	3.83	3.22	12.68	6.73	5.62	6.43	3.37
4	4.06	2.70	6.02	10.87	13.56	8.27	9.42	8.93	8.16	4.46	5.35	5.23	13.93	7.17	9.61	7.85	3.33
5	4.06	5.49	6.61	10.84	12.65	6.99	9.64	11.70	9.65	6.49	7.42	5.46	14.41	8.53	11.08	8.73	2.99
6	4.32	7.17	6.42	10.68	12.34	6.32	12.19	16.75	11.64	9.75	12.16	5.76	15.68	9.95	13.70	10.32	3.71
7	3.82	7.60	4.28	8.50	11.75	5.68	8.93	8.45	11.43	8.89	11.41	3.74	7.60	9.06	10.72	8.12	2.71
9	4.74	6.83	3.71	6.28	9.61	4.27	8.12	6.19	9.97	6.80	8.79	3.57	7.41	6.42	8.70	6.76	2.05
12	5.61	8.07	2.36	5.66	8.08	3.49	7.05	4.70	7.78	5.00	7.00	6.25	3.75	4.83	6.49	5.74	1.73
24	2.57	3.56	0.85	2.48	4.78	1.39	2.51	1.83	3.48	2.19	2.32	2.30	3.67	2.29	2.64	2.59	0.97
36	1.24	1.53	0.61	1.64	3.01	0.63	1.73	1.16	2.38	1.42	1.64	1.24	1.74	1.26	1.26	1.50	0.61
48	0.80	0.76	0.27	0.98	2.13	0.29	1.05	0.95	1.54	1.06	1.10	0.63	1.33	0.73	0.88	0.97	0.47
60	0.55	0.70	BLOQ	0.64	1.43	0.28	0.73	0.43	0.88	0.73	0.92	0.28	0.78	0.48	0.70	0.64	0.33
72	0.40	0.52	BLOQ	0.50	1.21	BLOQ	BLOQ	0.38	0.68	0.51	0.53	BLOQ	0.62	BLOQ	0.39	0.38	0.34

Plasma Fenofibric Acid Concentration (mg.ℓ vs. time (h) After Administration at 3 Capsules of the Conventional Form (Total amount of Fenofibrate administered: 300 mg)

Post-dose time (h)	1	2	3	4	5	6	8	9	10	11	12	13	14	15	16
0	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ
1	BLOQ	BLOQ	BLOQ	0.25	BLOQ	BLOQ	1.90	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ	BLOQ
2	BLOQ	BLOQ	0.25	4.67	0.34	1.52	5.83	BLOQ	BLOQ	0.42	0.63	BLOQ	BLOQ	BLOQ	1.28
3	1.76	0.99	2.16	7.39	4.51	3.72	5.89	2.45	1.53	1.71	1.55	1.03	1.40	0.47	3.79
4	3.24	4.62	5.57	9.13	8.83	5.00	5.76	5.12	6.54	4.37	3.58	3.47	4.75	1.48	5.08
5	4.53	10.24	12.20	12.16	10.43	4.77	6.57	11.97	12.91	4.93	6.94	4.22	6.40	3.55	11.35
6	8.77	17.36	12.93	12.08	13.18	5.66	6.62	14.17	18.00	9.03	11.45	4.30	11.12	10.65	17.47
7	4.75	11.92	12.12	10.71	11.36	4.84	5.90	12.31	14.42	8.08	10.58	4.17	13.21	10.11	16.35
9	3.64	8.21	9.29	8.39	9.62	6.34	5.80	7.33	10.86	6.37	8.25	6.34	10.22	7.21	11.79
12	4.24	7.03	6.20	6.90	7.96	8.66	5.30	6.67	7.50	5.11	7.09	12.05	9.16	5.74	8.06
24	2.36	3.43	1.88	3.12	4.76	2.53	2.19	2.61	2.85	2.66	2.85	6.53	4.92	2.29	3.08
36	1.17	2.03	0.92	1.56	3.27	0.95	1.47	1.14	1.73	1.48	1.38	3.31	2.31	1.33	1.69
48	0.70	1.17	0.61	1.02	2.06	0.49	0.71	0.94	0.90	1.07	0.92	1.72	1.39	0.81	1.03
60	0.49	0.50	0.43	0.66	1.77	0.31	0.74	0.81	0.58	0.69	0.55	0.81	1.13	0.54	0.74
72	BLOQ	BLOQ	0.30	0.49	1.48	BLOQ	0.49	0.54	0.34	0.52	0.40	BLOQ	0.83	0.35	0.40

The bioavailability, as measured by the extent of absorption (AUC) indicates, that 3 capsules of Example 1 of the present invention (201 mg of fenofibrate AUC = 195) are bioequivalent to 3 capsules of the conventional form (300 mg of fenofibrate AUC = 221).

That is, the bioavailability of fenofibrate from the composition of Example 1 of the present invention is 1.5 times higher than the bioavailability of fenofibrate of the conventional form.

EXAMPLE 2

Fenofibrate	5 kg
Gelucire® 44/14	7.5 kg
Carbowax 20,000	1.5 kg
Hydroxypropylcellulose	2.5 kg
	16.5 kg

To a heated kettel, 7.5 kg of Gelucire® 44/14 and 1.5 kg of carbowax 20,000 were added and then heated at 85°C until all components are molten. 5 kg of fenofibrate was added slowly while continuously stirring. When all the fenofibrate was dissolved, 2.5 kg of hydroxypropylcellulose was added and agitation was maintained for about twenty minutes. Using a liquid filing capsule machine with dosing pumps heated at 85°C, capsules of size 0 were filled with 660 mg of solution. Upon cooling at room temperature the capsules were packaged in bottles. Each capsule so

prepared contained 200 mg of fenofibrate. 12,701 capsules were produced and individually weighed. Results of the capsule weighing is shown in Table 3.

TABLE 3 Capsules Weight Variations From 12,701 Capsules	
Theoretical Weight	764.5 mg
Mean weight of acceptable capsules (95-105%)	763.9 mg
Standard Deviation of Accepted Capsules	6.9 mg
Relative Standard Deviation of Accepted Capsules	0.9%
Percent of Rejected Capsules (below 95% of Theoretical Amount)	0.307%
Percent of Rejected Capsules (above 105% of Theoretical Amount)	0.039%

It may readily be appreciated from Table 3 that the filling process of the present invention is extremely accurate.

PHARMACOKINETICAL STUDY

The composition of Example 2 of the present invention was compared during a Pharmacokinetical study to the co-micronized formulation available on the French market (Lypanthyl 200 M®).

The study was conducted as a single dose, randomized, four-way cross over study in 8 healthy subjects. The

subjects were randomly assigned to one of four administration sequences. On each of the four sessions, separated by wash-out periods of 7 days, the subjects received either 200 mg of fenofibrate under the form Lypantyl 200 M® or 200 mg of fenofibrate under the form of Example 2 with and without a high-fat breakfast. Blood samples were taken before and at different times up to 72 hours after administration. The plasma concentrations of fenofibric acid was determined in the samples using on HPLC Method..

The pharmacokinetics parameters obtained are shown in Table 4.

TABLE 4 Pharmacokinetical Parameters After Administration of Lypantyl 200 M® and Composition of Example 2 Taken With and Without a High Fat Breakfast (Dose 200 mg of Fenofibrate)

	Without Food		With Food	
	Example 2	Lipanthyl 200M®	Example 2	Lypanthyl 200M®
AUC_{0-72}	107.0	101.0	181.0	184.7
C_{max}	5.1	5.9	11.1	10.9
T_{max}	5.9	5.2	5.2	5.7

The present composition may thus be advantageously used to treat hyperlipidemia and/or hypercholesterolemia in humans. Generally, the effective daily amount of fenofibrate from humans ranges from about 100 mg to 600 mg per day, and preferably from about 100 to 300 mg per day, with the precise amount being determined by the attending

physician, considering such parameters as condition severity and body weight, for example.

Having fully described the present invention, it will be apparent to one of ordinary skill in the art that many changes and modification may be made to the above-described embodiments without departing from the spirit and scope of the present invention.

CLAIMS

1. A pharmaceutical composition for treating hyperlipidemia or hypercholesterolemia or both in a mammal, which comprises an effective amount of each of fenofibrate and an excipient comprising one or more polyglycolyzed glycerides.

2. The composition of Claim 1, wherein said fenofibrate is present in an amount of 5% to 95% by weight based on the total weight of the composition.

3. The composition of Claim 1, wherein the polyglycolyzed glycerides have a HLB value of at least 10.

4. The composition of Claim 3, wherein the polylglycolyzed glycerides have a HLB value of from 12 to 15.

5. The composition of Claim 1, which further comprises polyalkylene glycols to adjust the HLB value or melting point or both to the desired value.

6. The composition of Claim 1, wherein a suspension stabilizer is added.

7. The composition of Claim 6, wherein said suspension stabilizer is selected from the group and consisting of cellulose, povidone, poloxamers, α, Ω-hydroxy-poly(oxyethylene) poly(oxypropylene)-poly(oxyethylene)bloc polymers.

8. The composition of Claim 1, in which said fenofibrate and said excipient are in unit dosage form and are contained in a hard gelatin capsule.

9. The composition of Claim 8, wherein said hard gelatin capsule contains from about 67 mg to about 200 mg of fenofibrate.

10. A method of making a solid oral dosage form of a pharmaceutical composition, comprising an effective amount of each of fenofibrate and an excipient comprising one or more polyglycolyzed glycerides, which method comprises adding said molten fenofibrate and said excipient to hard gelatin capsules, and allowing said said molten fenofibrate and said excipient to cool therein.

11. A method of treating hyperlipidemia or hypercholesterolemia or both in a mammal in need threof, which comprises administering to said mammal an effective amount of a pharmaceutical composition, comprising fenofibrate and an excipient containing one or more polyglycolyzed glycerides.

12. The method of Claim 11, wherein said mammal is human, and said effective amount of fenofibrate in said composition is from about 100 mg to 600 mg per day.

13. The method of Claim 12, wherein said effective amount of fenofibrate in said composition is from about 100 mg to 300 mg per day.

14. The method of Claim 11, wherein said composition is administered orally.

15. The method of Claim 10, which is with the proviso that the fenofibrate used is not co-micronized.

INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/BE 96/00002

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/22 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,95 24893 (R. P. SCHERER LTD.) 21 September 1995 see claim 1 see page 13, line 5 - page 15, line 7 see page 25, line 3 - line 4 see page 44; example 6 -----	1-4,6-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
29 March 1996	11. 04. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Ventura Amat, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

rnational application No.

PCT/BE 96/ 00002

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 11-14 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

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(54) Title: IMPROVED PHARMACEUTICAL COMPOSITION CONTAINING A PPAR ALPHA AGENT AND A PROCESS FOR PREPARING IT

(57) Abstract: Oral semi-solid or liquid composition for treating hyperlipidemia or hypercholesterolemia in humans, which comprises at least an effective amount of peroxisome proliferator activated receptor alpha agent (PPARa), one polyglycolized glyceride and one hydrophilic disintegrating agent.

Improved pharmaceutical composition containing a PPAR alpha agent and a process for preparing it

ABSTRACT

An oral semi-solid composition containing at least one peroxisome proliferator activated alpha agent (PPARα) at a therapeutical dose, a polyglycolized glyceride and an hydrophilic disintegrating agent.

BACKGROUND OF THE INVENTION

Fibrates are old hypolipidemic drugs with pleitropic effects on lipid metabolism. Their intimate molecular mechanisms of action have been mysterious for a long time. Recently, it has been shown that the pharmacological effect of fibrates depends on their binding to "Peroxisome Proliferator Activated Receptor alpha" (PPAR alpha). The binding of fibrates to PPAR induces the activation of the inhibition of multiple genes involved in lipid metabolism through the binding of the activated PPAR alpha to "Peroxisome Proliferator Response Element" (PPRE) located in the gene promoters. Furthermore, it was recently demonstrated that fibrates are potent antiinflammatory molecules through an indirect modulation of the nuclear-factor-Kappa B activity.

Fenofibrate or P-(4-chlorobenzoyl)-phenoxy isobutyrate isopropyl ester is useful for the treatment of adult patients with very high elevations of serum triglyceride levels and/or cholesterol levels. Initially, the usual daily dosage was 300 mg which was administered in two or three doses. A few years later, a suprabioavailable composition of fenofibrate was developed and marketed by Laboratoires Fournier, France (EP 0030532). 200 mg of fenofibrate from this composition was bioequivalent to 300 mg of the initial composition. Fenofibrate is absorbed as fenofibric acid which is responsible

for the pharmacological activity. Fenofibric acid resulting from the hydrolysis of fenofibrate is extensively bound to plasma albumin. The plasma half-life is about 20 hours. Fenofibric acid is excreted predominantly in the urine, mainly as the glucuronide conjugate, but also as a reduced form of fenofibric acid and its glucuronides.

Fenofibrate is presently available in a pharmaceutical dosage form consisting of hard gelatin capsules containing fenofibrate, lactose starch and magnesium stearate. After oral administration, during a meal, about 60% of the dose of this conventional form is effectively absorbed and found in the blood as fenofibric acid, the main metabolite responsible for pharmacological activity.

The first attempt to improve the bioavailability of fenofibrate was performed by Ben-Armor et al, by solubilizing the fenofibrate in dimethyl isosorbide, a nonaqueous solvent with a miscible wetting agent (Labrafil M1944CS) with HLB of between 3-4. In order to use the product in capsules, colloidal silicon oxide was added to increase the viscosity. The liquid so obtained was placed in hard gelatin capsules which, to be leak proof, were sealed. In vivo studies with this formulation indicate that there was no statistically significant difference in bioavailability between this liquid formulation and the conventional form when the product was given with food.

European Patent Application 0330532 discloses a fenofibrate composition wherein the fenofibrate powder is co-micronized with a solid wetting agent. Sodium lauryl sulfate is described as the solid wetting agent of choice. The co-micronized powder so obtained is mixed with capsule filling excipient such as lactose, starch, polyvinyl pyrollidone and magnesium stearate. A formulation of this composition is actually available on the French market under the trade name Lypanthyl® 200, Fournier, France. A study comparing this formulation (Lypanthyl® 200) to the conventional form was undertaken and a statistically significant increase in bioavailability was indicated for the

former. In particular, it was found that 67 mg of the new form gives the same amount absorbed as does 100 mg of the conventional form.

Unfortunately, co-micronization of the active drug fenofibrate with the wetting agent sodium lauryl sulfate, although necessary, is a time consuming and costly operation. Further, an inherent drawback of micronization is that the material obtained must comply with very stringent particle size specifications. Indeed, the solubility and thus bioavailability depend on the particle size, whereby the presence of only some larger fenofibrate particles in a dosage form containing 160mg could modify greatly the solubility and bioavailability.

The Canadian patent 2,214,895 describes an improved formulation of fenofibrate obtained by making a solid dispersion of fenofibrate and a disintegrating agent.

Moreover, the filling of hard gelatin capsules with a micronized powder is a difficult operation, particularly if weight variation homogeneity is considered.

Hence, a need exists for a fenofibrate formulation that avoids the use of co-micronization, while providing a bioavailability comparable to that afforded by the conventional fenofibrate formulation which uses co-micronization.

Consequently, there was a need to dispose of a fenofibrate composition easy to manufacture and providing a high bioavailability after oral intake. Such a composition is disclosed in US patent 5,545,628 based on a semi-solid formulation containing fenofibrate and an excipient containing one or more polyglycolized glycerides.

But, more recently, after that, the US patent 6,277,405 describes a composition of fenofibrate allowing to still improve the bioavailability of fenofibrate after oral intake. This patent describes the use of:

a) an inert hydrosoluble carrier covered with at least one layer containing fenofibrate active ingredient in a micronized form having a size smaller than 20 microns (µm), a hydrophilic polymer and, optionally, a surfactant, said hydrophilic polymer making up at least 20% by weight of an (a) and :
b) optionally one or several outer phase(s) or layer(s).

The composition described in the US patent 6,277,405 allows indeed to improve the bioavailability of fenofibrate in comparison with the commercial forms available on the market for several years (TRICOR® 200, LIPIDIL® 200, LIPANTHYL® 200, Fournier, France) and corresponding to the older US patent EP 0330532.

Pharmacokinetic studies have demonstrated that 200 mg of the commercial formulation are equivalent to 160 mg of the composition corresponding to the patent 6,277,405 (i.e. a 20% increase of bioavailability), which is already commercialized in several countries (LIPIDIL® 160, LIPANTHYL® 160).

Nevertheless, the process and the composition described in the patent 6,277,405 are complex, difficult and long to manufacture, and expensive. There was therefore still a need for a fenofibrate oral composition allowing to reach a similar bioavailability as that of US patent 6,277,405 but with a simpler and cheaper manufacturing process. The formulation described in US patent 5,545,628 did not offer a sufficient bioavailability. Indeed, this kind of composition gives a bioavailability similar to that of Tricor® 200 mg but 20% inferior to the LIPIDIL® 160 mg.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a PPARα agent containing composition (preferably a fenofibrate containing composition) with a very high bioavailability, which can be prepared without requiring micronisation and/or the presence of an hydrophilic polymer and/or the necessity of an outer phase layer. It is also an object of the invention to describe an easy, reliable and cheap process for manufacturing the new composition.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Oral semi-solid pharmaceutical compositions present various advantages:

The advantages of the semi-solid formulations are multiple for a PPAR derivative: protection of the active ingredient from air and humidity, possibility of increasing the dissolution rate of the molecule and hence of bioavailability, diminution of the risk of contamination of the operator, diminution of the risk of cross contamination, no possibility of demixing under the effect of vibrational mixing during manufacturing process, facility of the production process. The choice of the nature of the formulation of course influences the stability of the pharmaceutical form and the bioavailability of the drug contained in it. Generally, a maximum bioavailability is achieved by preparing and keeping the drug in the amorphous/solubilized state in a solid dispersion or in a lipid-based formulation. For these systems, the barrier we are avoiding is the compound « washing-out » of solution to a large extent into a insoluble crystalline form during the dissolution/release step in vivo.

The use of polyglycolized glycerides in this kind of semi-solid compositions has already been described in US patent 5,545,628, the content of which is incorporated to the present specification by reference.

It has now been observed that by using simultaneously a polyglycolized glyceride and a disintegrating agent in a semi-solid or liquid fenofibrate composition, it was possible reach the bioavailability and the mean plasma concentration of the commercial Lipidil ® formulation, the latter formulation requiring a co-micronization step as taught in EP 0330532.

The present invention provides a pharmaceutical formulation for treating hyperlipidemia and/or hypercholesterolemia in a mammal, which contains an effective amount of a PPARα agent or a mixture of PPARα agents, advantageously fenofibrate, an excipient which contains one or more polyglycolyzed glycerides, the polyglycolyzed glycerides preferably having an HLB value of at least about 10, and one disintegrating agent.

PPAR agents are agents having a "peroxisome proliferation activated receptor activating effect", i.e. agents activating the binding of PPAR to peroxisome proliferator response element (PPRE), as well as agents activating the PPAR for its binding to PPRE.The agent as such, or a metabolite thereof , or a compound generated by the organism due to the presence of the agent is bound to the PPAR, whereby inducing the binding of PPAR to PPRE.

PPAR agents (alpha, delta and/or gamma) are agents for which the data determined by measuring the receptor-activating effect of a certain compound are statistically judged as being significantly different from the control data determined in the absence of the compound. Many documents disclose PPAR agents. For example, reference can be made to US 6,365,586;US 6,331,627 ; US 6,214,820, etc. disclosing or referring to such agents.

In the composition of the invention, the PPAR agent is advantageously an agent with a low water solubility, such as a water solubility similar or smaller

to the water solubility of fenofibrate (for example a water solubility expressed in g/l corresponding to less than 5 (preferably less than 2) times the solubility of fenofibrate in water (pH 7, temperature 20°C).

The PPAR agent is more precisely a PPARα agent, such as a compound of the fibrate family, such as fenofibrate, ciprofibrate, Clofibrate, Gemfibrozil, Bezafibrate or combinations thereof, fenofibrate and combinations containing fenofibrate being most preferred.

The present invention is also particularly advantageous for the production of oral solid dosage forms which can be prepared by melting the excipients in which the fenofibrate is at least partially soluble, whereby particle size specifications are not required.

Advantageously, the present invention also relates to the addition of a suspension stabilizer to the molten solution of PPARα (such as fenofibrate)-polyglycolyzed glycerides. The suspension stabilizer avoids the formation of PPARα crystals, such as fenofibrate crystals, during the cooling of the filled hard gelatin capsules. Suitable suspension stabilizers which may be used are, for example, cellulose derivatives, such as hydroxypropylcellulose, hydroxypropylmethyl cellulose, methyl cellulose, and hydroxyethylcellulose, povidone, poloxamers, .alpha., .OMEGA.-hydroxy-poly(oxyethylene) poly(oxypropylene)-poly(oxyethylene)bloc polymers. Other suspension stabilizers equivalent to these stabiliers may, of course, also be used.

The present invention is also particularly advantageous for the production of a pharmaceutical composition in that the hot, homogeneous PPARα (such as fenofibrate) solution is filled in hard gelatin capsules. This filling process permits to ensure a very precise PPARα (such as fenofibrate) amounts in each capsule.

The present invention is particularly advantageous as well for the production of the present pharmaceutical composition in that the process for manufacturing the composition requires very few steps such as melting, mixing and filling. This renders the present manufacturing process extremely cost effective when compared to one using co-micronization of powders.

Polyglycolyzed glycerides which may be used in the present invention are generally mixtures of known monoesters, diesters and triesters of glycerols and known monoesters and diesters of polyethylene glycols with a mean relative molecular mass between about 200 and 6000. They may be obtained by partial transesterification of triglycerides with polyethylene glycol or by esterification of glycerol and polyethylene glycol with fatty acids using known reactions. Preferably, the fatty acid component contains 8-22 carbon atoms, particularly 10-18 carbon atoms. Examples of natural vegetable oils which may be used include palm kernel oil and palm oil. However, these are only examples. The polyol suitably has a molecular weight in the range of about 200-6000 and preferably contains polyethylene glycol, although other polyols may be employed, such as polyglycerols or sorbitol. They are available on the market under the trade name Gelucire® (Gattefossé, France).

As noted above, the HLB of the polyglycolized glycerides is preferably at least about 10, and more preferably between about 12 and 15. The melting point of the polyglycolized glycerides may be between about 18.degree. C. and 60.degree. C. However, it is especially desirable to use polyglycolized glycerides having a melting point above 30.degree. C., and preferably above 35.degree. C., since there is no need for sealing the capsule, to assure the leak proofness thereof, when such excipients are used.

Further, two or more polyglycolized glycerides may be mixed in order to adjust both the HLB value and the melting point to a desired value. The

HLB value and melting point of the composition may further be adjusted with the addition of components such as polyethylene glycols, polyoxyethylene glycols fatty acid esters, and fatty acid alcohols. In view of the present specification, it is well within the skill of the artisan to mix the polyglycolized glycerides to obtain desired HLB values and melting points.

Although the present invention is not bind by any particular theories, one plausible mechanism of operation for the present invention is that upon cooling, the melted mixture of hot PPARα (such as fenofibrate)-polyglycolized glycerides maintains the PPARα (such as fenofibrate) in liquid form. When absorbed in the gastrointestinal tract of a patient, the gastrointestinal fluids are able to dissolve the PPARα (such as fenofibrate) due to the HLB value of the excipient mixture, whereby PPARα (such as fenofibrate) is readily absorbed.

The release of the drug from this kind of semi-solid lipophilic matrix is operated by a phenomenon of erosion-diffusion of the form when it is in contact with the gastro-intestinal fluids. As most excipients have relatively lipophilic properties, the release of the drug from the composition is relatively slow.

It was consequently a goal of the present invention to increase the either the rate of release or the nature of the particles release (size) of PPARα (such as fenofibrate) from this kind of composition.

Surprisingly enough, this increase of release has been obtained by adding in the formulation very hydrophilic excipients (disintegrating agents) not soluble in the fatty mass. Such hydrophilic excipients may be the following ones but are not restricted to them: sodium starch glycolate, sodium croscarmellose, crospovidone, pregelatinized starch, maize starch, Aerosil® (colloidal silicone dioxide). This increase of the rate or quality of release of

the drug with formulations containinga disintegrant in a semi-solid formulation is quite surprising since disintegrants are usually used in tablets formulations wherein the forces of compression are quite high.
These kinds of hydrophilic substances while not soluble are able to be dispersed homogeneously in the fatty mass and remain homogeneously dispersed after capsule filling and cooling.

The invention relates also to method for treating or preventing hyperlipidemia or hypercholesterolemia in a patient, in which at least an effective amount of a peroxisome proliferator activated receptor agent is orally administered to the patient simultaneously with at least one polyglycolized glyceride and one hydrophilic disintegrating agent. In this method, the PPAR agent, the polyglycolized glyceride and the disintegrating agent are preferably of the type disclosed for the composition of the invention.

The invention further relates to a process for the preparation of an oral semi-solid or liquid composition containing at least an effective amount of PPAR agent, at least one polyglycolised glyceride and one hydrophilic disintegrating agent, in which the PPAR agent in powder form and hydrophilic disintegrating agent are mixed to a molten mixture containing at least one polyglycolised glyceride.
Advantageously, the PPAR agent and the hydrophilic disintegrating agent are mixed successively with the molten mixture.
Preferably, the PPAR agent is first mixed with the molten mixture, and before adding the hydrophilic disintegrating agent, the homogeneous dispersion of the PPAR powder in the molten mixture is controlled

The weight ratio polyglycolized glyceride(s)/hydrophilic disintegrating agent in the composition of the invention or in the method of the invention or in the process of the invention is for example comprised between 100 and 0.1,

advantageously between 50 and 2, preferably between 40 and 4, for example between 8 and 25.

The weight ratio PPAR agent/hydrophilic disintegrating agent in the composition of the invention or in the method of the invention or in the process of the invention is for example comprised between 100 and 0.1, advantageously between 50 and 2, preferably between 40 and 4, for example between 6 and 25.

The weight ratio PPAR agent/polyglycolized glyceride(s) in the composition of the invention and in the method of the invention or in the process of the invention is for example comprised between 10 and 0.1, advantageously between 5 and 0.5, preferably greater than 1, such as between 1.1 and 2, for example 1.2, 1.5, etc.

BRIEF DESCIPTION OF THE DRAWINGS

Figure 1 is a graph showing the in vitro comparative dissolution profiles of 2 semi-solid formulations of fenofibrate with and without disintegrant

Figure 2 is a graph showing the in vitro comparative dissolution profiles of 2 semi-solid fenofibrate compositions containing different disintegrating agents

Figure 3 is a graph showing the pharmacokinetic results of comparative study in 18 volunteers for fenofibrate (log-transformed data).

EXAMPLES

An example of preferred manufacturing process is given hereinbelow:

The manufacturing process allowing to obtain the composition described in the present invention is, for example, as given hereinbelow. In this example, fenofibrate is used as example of PPARα agent.

Melt the Gelucire® 44/14 and PEG in an adequately equipped mixer for liquid (TRIAGI, LLEAL Barcelone, Spain, or FRYMA, Basel, Switzerland) at 75°C. Add the fenofibrate powder to the molten mix. Continue the mixing while mounting the temperature of the mix to 75°C. Once fenofibrate is homogeneously dispersed in the mass, add the hydropropylcellulose at 75°C and under mixing. Finally add the disintegrating agent at 75°C and under mixing. The disintegrating agent is not dissolved in the fatty excipients but is homogeneously dispersed in the mass. Start the filling of hard gelatine or hypromellose capsules (at 70°C). Allow the capsules to cool until 30°C. At this temperature, the product becomes solid. Package adequately the capsules.

Different examples of compositions 1 to 5 are given hereinbelow:

Fenofibrate	200
Saturated polyglycolized glycerides (Gelucire 44/14)	250
Polyethyleneglycol (PEG) 8000	55
Hydropropylcellulose (HPC)	95
Sodium starch glycolate (Explotab)	20
	620 mg (composition 1)

Fenofibrate	267
Saturated polyglycolized glycerides (Gelucire 44/14)	290
Polyethyleneglycol (PEG) 8000	55
Hydropropylcellulose (HPC)	95
Polyplasdone XL (PLPXL)	20
	727 mg (composition 2)

Fenofibrate	200
Saturated polyglycolized glycerides (Gelucire 44/14)	290
Polyethyleneglycol (PEG) 10000	30
Polyethyleneglycol (PEG) 20000	30
Hydropropylcellulose (HPC)	90
Sodium starch glycolate (Explotab)	20
	660 mg (composition 3)

Fenofibrate	160
Saturated polyglycolized glycerides (Gelucire 44/14)	240
Polyethyleneglycol (PEG) 20000	48
Hydropropylcellulose (HPC)	95
Sodium starch glycolate (Explotab)	20
	563 mg (composition 4 or Fenogal ® Lidose ®)

Fenofibrate	200
Saturated polyglycolized glycerides (Gelucire 44/14)	300
Polyethyleneglycol (PEG) 20000	55
Hydropropylcellulose (HPC)	95
Croscarmellose (AC-DI-SOL)	20
	670 mg (composition 5)

Compositions similar to compositions 1 to 5 have been prepared by replacing the fenofibrate powder by other PPAR agents, namely clofibrate, bezafibrate, ciprofibrate, gemfibrozil, mixtures of PPAR agents, such as mixture of bezafibrate (10-90%) + fenofibrate (90-10%). The following composition 6 is a specific example of composition containing clofibrate.

clofibrate	300
Saturated polyglycolized glycerides (Gelucire 44/14)	340
Polyethyleneglycol (PEG) 20000	80
Hydropropylcellulose (HPC)	125
Sodium starch glycolate (Explotab)	20
	865 mg (composition 6)

Effect of the presence of an disintegrating agent

An in vitro dissolution test has been performed to assess if the presence of a disintegrating agent in the formulation allowed to increase the release and / or the dissolution of fenofibrate. As seen in figure 1, the presence of 3 % of sodium strarch glycolate clearly increases the dissolution rate of fenofibrate.

In said figure 1, the in vitro comparative dissolution profiles of 2 semi-solid formulations of fenofibrate with and without disintegrant are shown.

The dissolution method used for said comparative study is described herebelow.

- Volume of dissolution: 900 ml
- Test temperature: 37.0 ± 0.5°C.
- Paddle rotation speed: 100 rpm.
- Test duration: 180 minutes.
- Detection : UV at 288 nm.
- Blank : dissolution medium.
- n = 6 vessels / test

The dissolution medium was 900 ml of an acidic (pH 1.2) dissolution medium containing Polysorbate 80 (2 %) as surfactant and pepsin (3.2 g/l) as enzyme.

Effect of the type of disintegrating agent

It was also interesting to assess if different disintegrating agents substances were able to increase the release and/or dissolution of fenofibrate in vitro in comparison in the same way. Therefore, the dissolution profile of a semi-solid formulation of fenofibrate containing 4% of sodium starch glycolate was compared with a semi-solid formulation of fenofibrate containing 4% of sodium croscarmellose.

Figure 2 shows the in vitro comparative dissolution profiles of 2 semi-solid fenofibrate compositions containing different disintegrating agents (dissolution method – see hereinabove).
It appears from said figure that sodium croscarmellose and sodium starch glycolate give similar increase of dissolution rate.

But an increase of the dissolution rates does not mean that the composition corresponding to the present invention allows to increase the bioavailability of fenofibrate in humans after an oral administration. Therefore, pharmacokinetic studies have been performed:

In vivo test

The bioavailability of FENOGAL® LIDOSE® 160 mg capsule (Laboratoires SMB SA) has been assessed and compared to the bioavailability of the reference (LIPIDIL-TER® 160 mg tablet, Fournier) on 18 healthy subjects. LIPIDIL-TER® 160 mg tablet is a suprabioavailable formulation of

fenofibrate wherein the higher bioavailability of the drug is obtained by co-micronizing the fenofibrate together with a surfactant. LIPIDIL-TER® 160 mg is already on the market in several countries.

This study (SMB-FENO-SD012) was a single dose, two treatments, two periods, two sequences, randomised, cross-over and with at least 8 days wash-out between the two periods.

The subjects were healthy Caucasian volunteers of both sexes (non-pregnant, non-breast-feeding), aged 18 to 50 years, non smokers or smoking less than 10 cigarettes per day.

The drugs (one tablet or one capsule containing 160 mg of fenofibrate in one intake during the two periods) were taken with food (a standardized breakfast).

Blood samples were collected according to the following sampling schedule: pre-dose and 1h, 2h, 3h, 4h, 5h, 6h, 7h, 9h, 12h, 24h, 36h, 48h, 60h and 72 hours post-dose.

The plasma concentrations of fenofibrate were quantified using a fully validated LC/MS/MS method.

The figure 3 describes the mean pharmacokinetic profile of fenofibrate for the two formulations (n=18 subjects).

The continuous variables (AUC_T, AUC_∞, C_{max}, $t_{1/2}$ and MRT) were evaluated according to an univariate ANOVA based on log-transformed data. For T_{max}, the non parametric Kruskal-Wallis test was used. Bioequivalence was evaluated using the Shuirman two one-sided t-test (90% CI). The Kinetica Program (Innaphase®) has been applied for this calculations.

The table hereinbelow gives the value of the main pharmacokinetics results and statistical analysis obtained for each formulation of fenofibrate.

Table 1 : Pharmacokinetic results and statistical analysis of comparative study in 18 volunteers for fenofibrate (log-transformed data)

Results			Bioequivalence tests
Parameter	LIPIDIL-TER® 160 mg	FENOGAL® LIDOSE® 160 mg	Shuirman 90% CI Range (acceptance range : 80-125)
AUC_∞ ± SD	173.29 (µg.h/ml) ± 90.82	172.43 (µg.h/ml) ± 85.78	94-105
AUC_T ± SD	161.21 (µg.h/ml) ± 74.30	160.42 (µg.h/ml) ± 70.52	94-105
C_{max} ± SD	9.54 (µg /ml) ± 1.97	9.12 (µg /ml) ± 2.10	88-103
T_{max} ± SD	4.17 (h) ± 1.38	4.50 (h) ± 0.98	/
$t_{1/2}$ ± SD	15.57 (h) ± 4.56	15.58 (h) ± 4.37	95-106
MRT ± SD	23.05 (h) ± 7.14	23.91 (h) ± 6.92	99-110

This study demonstrated that LIPIDIL-TER® 160 mg and FENOGAL® LIDOSE® 160 mg are bioequivalent after a single oral dose administration of each product in fed conditions. Indeed, the pharmacokinetics parameters AUC (AUC_∞ and AUC_T), C_{max} , T_{max} , $t_{1/2}$ and MRT were within the predetermined confidence interval. Consequently, the present invention

allows to obtain a similar suprabioavailable product as LIPIDIL-TER® 160 mg but with a very simplier and cheaper manufacturing process.

CLAIMS

1. An oral semi-solid or liquid composition for treating hyperlipidemia or hypercholesterolemia in humans, which comprises at least an effective amount of a peroxisome proliferator activated receptor alpha agent (PPARα), one polyglycolized glyceride and one hydrophilic disintegrating agent.
2. The composition of claim 1, wherein the PPARα is a compound of the fibrate family, preferably a compound selected from the group consisting of fenofibrate, ciprofibrate, clofibrate, gemfibrozil, bezafibrate and combinations thereof.
3. The composition of claim 1, wherein the PPARα agent is fenofibrate.
4. The composition of claim 1, wherein the PPARα is clofibrate.
5. The composition of claim 1 wherein the PPARα is bezafibrate or ciprofibrate.
6. The composition of claim 1, wherein the disintegrating agent is sodium starch glycolate.
7. The composition of claim 1, wherein the disintegrating agent is sodium croscarmellose, crospovidone, starch, colloidal silicone dioxide or another pharmaceutically accepted disintegrating agent.
8. The composition of claim 1 further containing a polyethylene glycol or a mix of polyethylene glycol with different molecular mass.
9. The composition of claim 1, wherein a suspension stabilizer is added in the composition.
10. The composition of claim 9, wherein the suspension stabilizer is a cellulose derivative.
11. The composition of claim 10, wherein the suspension stabilizer is hydropropylcellulose.

12. The composition of claim 3, wherein said fenofibrate is present in amount of 10% to 80% per weight based on the total weight of the formulation.

13. The composition of claim 3, wherein the amount of fenofibrate per dose is between 30 and 400 mg.

14. The composition of claim 1, wherein the composition is filled in hard gelatine capsules, hypromellose capsules or in other pharmaceutically acceptable capsules.

15. The composition of claim 2, which is with the proviso that the fenofibrate is not co-micronized.

16. The composition of claim 1, in which the weight ratio PPAR agent/hydrophilic disintegrating agent is comprised between 100 and 0.1, advantageously between 50 and 2, preferably between 40 and 4, more preferably between 6 and 25, while the weight ratio PPAR agent/polyglycolized glyceride(s) is comprised between 10 and 0.1, advantageously between 5 and 0.5, preferably greater than 1, more preferably between 1.1 and 2.

17. A method for treating or preventing hyperlipidemia or hypercholesterolemia in a patient, in which at least an effective amount of a peroxisome proliferator activated receptor agent is orally administered to the patient simultaneously with at least one polyglycolized glyceride and one hydrophilic disintegrating agent.

18. A process for the preparation of an oral semi-solid or liquid composition containing at least an effective amount of PPAR agent, at least one polyglycolised glyceride and one hydrophilic disintegrating agent, in which the PPAR agent in powder form and hydrophilic disintegrating agent are mixed to a molten mixture containing at least one polyglycolised glyceride.

19. The process of claim 18, in which the PPAR agent and the hydrophilic disintegrating agent are mixed successively with the molten mixture.

20. The process of claim 19, in which the PPAR agent is first mixed with the molten mixture, and in which before adding the hydrophilic disintegrating agent, the homogeneous dispersion of the PPAR powder in the molten mixture is controlled.

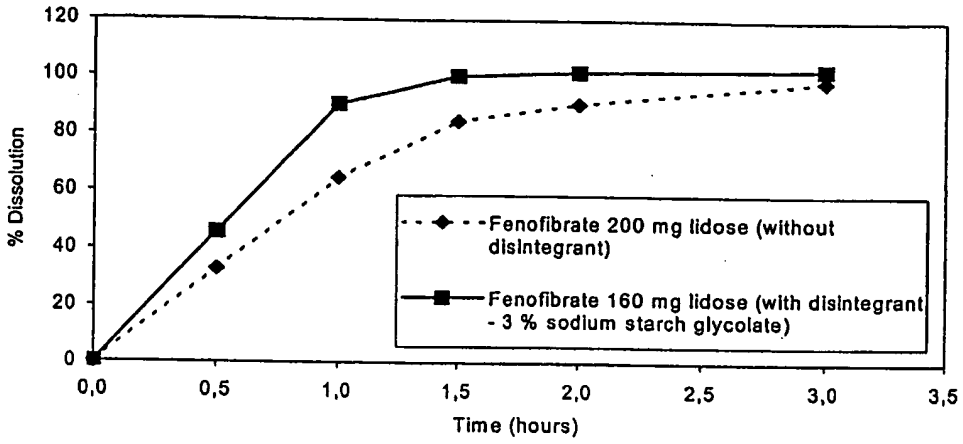


Figure 1

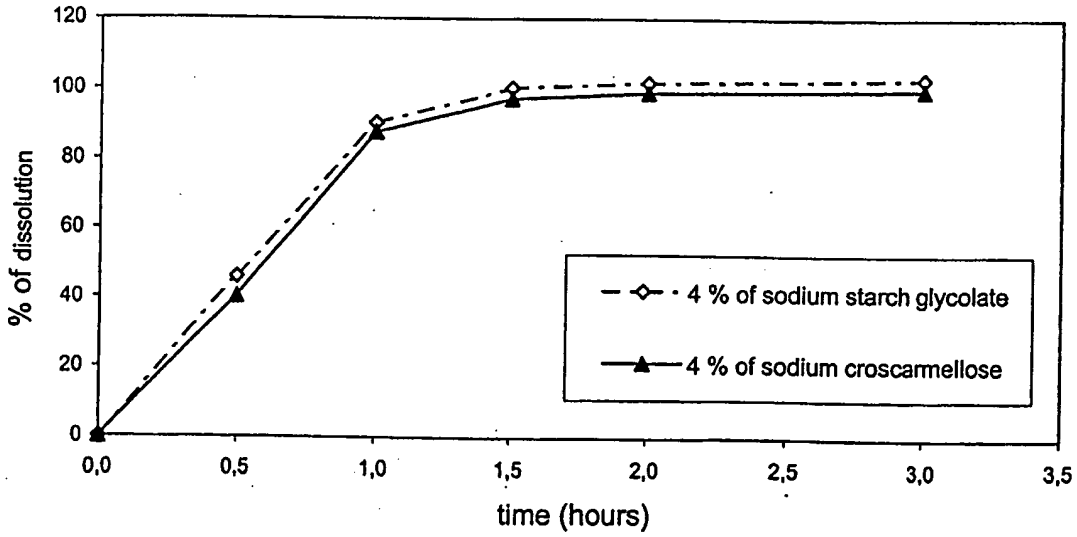
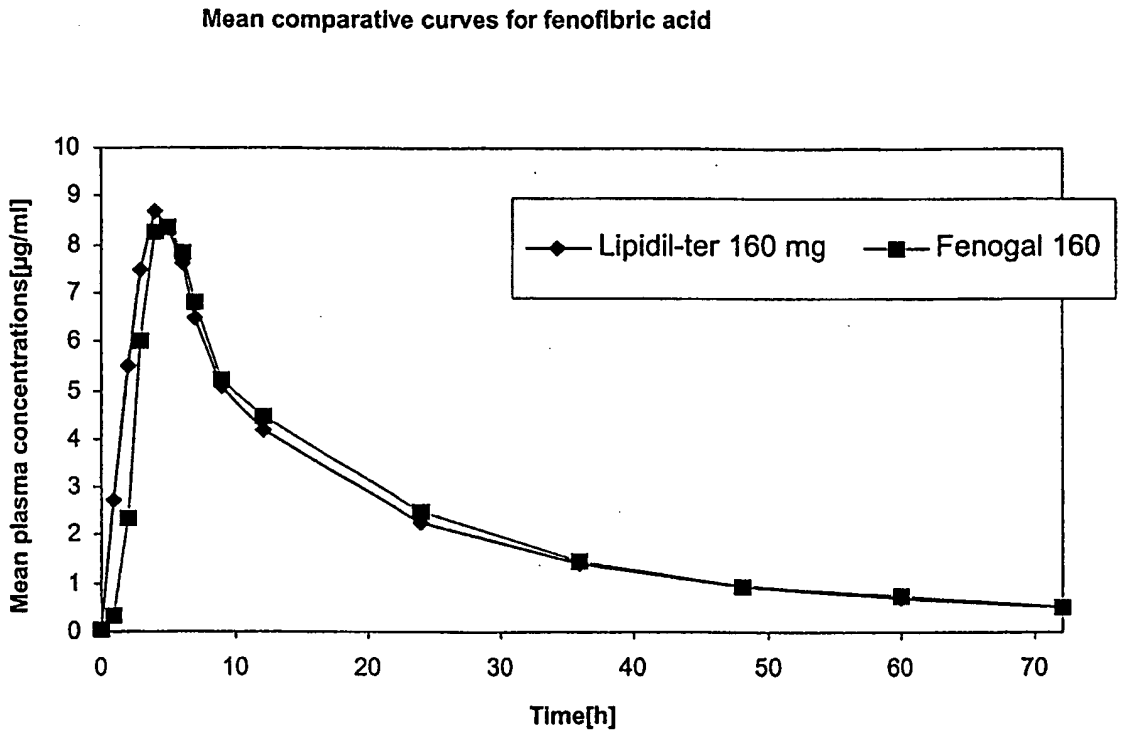


Figure 2


Mean comparative curves for fenofibric acid
Mean plasma concentrations[µg/ml]
Time[h]
Lipidil-ter 160 mg
Fenogal 160
0
1
2
3
4
5
6
7
8
9
10
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10
20
30
40
50
60
70

Figure 3

INTERNATIONAL SEARCH REPORT

Int ial Application No
PCT/BE 02/00123

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/215 A61K9/48 A61K31/00 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 12528 A (SMB TECHNOLOGY) 18 March 1999 (1999-03-18) claims 1,9,10,12,14,16 page 7, line 17 -page 8, line 5 page 8, line 23 -page 9, line 7 page 9, line 26 -page 10, line 11	1-3, 7-15, 18-20
X	WO 01 21154 A (RTP PHARMA) 29 March 2001 (2001-03-29) claims 1,3,9-11 page 16, paragraph 4 -page 17 page 28	1-3, 7-15, 18-20

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 November 2002	12/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Peeters, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int[illegible]al Application No
PCT/BE 02/00123

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 59475 A (LIPOCINE) 12 October 2000 (2000-10-12) claims 1,4,21-24,48-50,53,69,74 page 27 page 45, line 28 -page 46, line 12 page 47, line 18-30 page 53, line 1-7	1,2, 7-10,14, 15,18-20

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

.....ational application No.
PCT/BE 02/00123

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 15 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Continuation of Box I.2

Present claims 1, 6-11, 14 and 16-20 relate to a product/compound/method defined by reference to a desirable characteristic or property, namely: "Peroxisome proliferator activated receptor alpha agent (PPAR-alpha)"

The claims cover all products/compounds/methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/compounds/methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product/compound/method by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely for claims 2, 3-5, 12, 13 15 and for the compounds cited in the examples, with due regard to the general idea underlying the present application .

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Int[illegible]al Application No
PCT/BE 02/00123

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9912528 A	18-03-1999	BE 1011363 A3	03-08-1999
		WO 9912528 A1	18-03-1999
WO 0121154 A	29-03-2001	AU 7984200 A	24-04-2001
		EP 1214059 A2	19-06-2002
		WO 0121154 A2	29-03-2001
WO 0059475 A	12-10-2000	US 6383471 B1	07-05-2002
		AU 3763700 A	23-10-2000
		EP 1165048 A1	02-01-2002
		WO 0059475 A1	12-10-2000

(19) Europäisches Patentamt
European Patent Office
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(11) Publication number: **0 012 523**
A1

(12) EUROPEAN PATENT APPLICATION

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(54) Therapeutic compositions with enhanced bioavailability and process for their preparation.

(57) The invention relates to new compositions of poorly soluble or water insoluble drugs and to compositions of relatively soluble drugs which have a tendency to agglomerate or crystallise in storage or after formulation into pharmaceutical dosage form. The new compositions provide higher dissolution rates of said drugs in vitro and increased bioavailability. The compositions of this invention comprise such poorly soluble, water insoluble or relatively soluble drugs, a non-toxic water soluble polymer and a wetting agent. A process for preparing the compositions is also disclosed. Compositions containing the known antifungal griseofulvin illustrate the invention.

EP 0 012 523 A1

This invention relates to compositions of poorly soluble or water insoluble drugs which provide poor bioavailability or are irregularly absorbed following oral administration of their solid dosage forms and to compositions of relatively soluble drugs which have a tendency to agglomerate or crystallise in storage or after formulation into pharmaceutical dosage form. More specifically, the herein disclosed invention relates to new pharmaceutical compositions of matter comprising such poorly soluble, water insoluble or relatively soluble drugs, a non-toxic water soluble polymer and a wetting agent. The invention further relates to a process for preparing the disclosed compositions which compositions provide a high order of drug bioavailability. In the main, the invention will be illustrated with the known antifungal griseofulvin.

Many drugs give an incomplete and irregular absorption when taken orally, particularly poorly water soluble or water insoluble compounds such as griseofulvin and many steroids. One of the earlier attempts to enhance the availability or bioavailability of such drugs relied on mechanical micronization of the pure compounds in order to decrease their particle size. While micronization did enhance absorption over the use of unmicronized material, absorption of the drug was still incomplete. Further the degree of micronization

which can be achieved is limited and the micronized particles tend to agglomerate, thus diminishing both the solubility of the drug and its bioavailability. U.S. Patent 2,900,304 is an illustration of griseofulvin compositions for oral or parenteral administration employing micronized drug particles.

Another approach for attempting to enhance the bioavailability of griseofulvin was studied by Marvel et al and teported in the Jl of Investigative Dermatology, 42, 197-203 (1964). Their studies related to the effect of a surfactant and particle size on the bioavailability of griseofulvin when orally administered. Results of their studies indicated that bioavailability of the drug was enhanced when administered in very dilute solutions or aqueous suspensions. Their results further tended to confirm that enhanced bioavailability was obtained with griseofulvin having a higher specific surface area, at least when administered in full daily divided doses. With respect to the effect of the surfactant sodium lauryl sulfate incorporated into griseofulvin tablets, their results demonstrated some initial enhancement of bioavailability with regularly particle sized drug and very little enhancement with micronized drug in comparison to surfactant-free tablets. These investigators further reported

that when the daily dose was divided, the surfactant had no enhancing effect.

Still another approach for the enhancement of drug bioavailability is represented by the work of Tachibana and Nakamura in Kollid-Zeitschrift and Zeitschrift Fur Polymere, 203, pgs. 130-133 (1965) and Mayershohn et al in the Journal of Pharmaceutical Science, 55, pgs. 1323-4 (1966). Both publications deal with the use of polyvinylpyrrolidone (PVP) for forming dispersions of a drug. Tachibana discusses the role of PVP in forming very dilute colloidal dispersions of β-carotene in PVP. Mayersohn further prepared solid dispersions or solid solutions of griseofulvin in PVP and the reported results show dissolution rates for the drug increasing with increasing proportions of PVP. This last publication further reported that in the absence of wetting agent in the dissolution medium, the enhancement of the dissolution rate is still greater.

Canadian Patent 987,588 of Riegelman et al, similarly discloses the use and process for making solid dispersions of a drug for enhancing its dissolution rate and bioavailability. In this case the solvents employed were polyethylene glycol (PEG) having molecular weights ranging from 4,000 to 20,000, pentaerythritol, pentaerythritol tetraacetate and monohydrous citric acid. Riegelman postulated that these solvents provided a matrice for griseofulvin which retards crystallization during the solidification process resulting in an ultramicrocrystalline form of the drug with correspondingly faster dissolution. Riegelman's results tend to support this finding of faster dissolution rates for solid solutions of griseofulvin over those of unmicronized, non-wetted micronized and wetted micronized griseofulvin. But his findings were limited to those solid solutions which contain less than 50 per cent by weight of the drug since the results demonstrated a slowing of the dissolution rate with higher concentrations of griseofulvin. Riegelman further concluded that the rate of dissolution for a composition having the same ratio of drug to solvent varies significantly depending on the method of preparation, with melt mixing at elevated temperatures in a volatile solvent providing the preferred mode or process.

Another process for preparing ultramicrocrystalline drug particles to increase dissolution of a drug is disclosed by Melliger in Belgian Patent 772,594.

That process is characterized by preparing a solution of the drug, PVP and urethane and subsequently removing the urethane. It was reported that, in general, satisfactory results were obtained using solutions in which the quantity of drug represented up to about 50per cent by weight of the quantity of PVP present.

U.S. Patent 3,673,163 and 4,024,240 respectively are further illustrations relating to the use of PVP in solid dispersions. In the first-cited patent, coprecipitates of acronycine with polyvinylpyrrolidone were prepared in proportions weighted to the polymer to increase the solubility of the coprecipitated acronycine. In the second-cited patent solid antibiotic dispersions containing the antibiotic designated A-32390, in proportions again weighted toward the PVP co-dispersant, were disclosed. Further examples of antibiotic combinations containing PVP are disclosed in U.S. Patent 3,577,514 wherein the PVP is used as a binding agent; and in U.S. Patents 3,485,914 and 3,499,959, wherein the PVP is used to sustain the release of the antibiotic. PVP has also been used as a stabilizer with nitroglycerin to retard migration between nitroglycerin tablets as disclosed in U.S. Patent 4,091,091.

With respect to processes employed in preparing certain PVP-griseofulvin compositions, Junginger in Pharm. Ind. 39, Nr. 4 at pgs. 384-388 and Nr. 5 at pgs. 498-501 (1977), reported that spray-dried products provided systems with higher energy levels in comparison with those of simple mixtures and coprecipitates, and correspondingly greater dissolution rates. Junginger further disclosed that the dissolution rates of the simple mixtures were higher when the PVP contents were increased.

In a further attempt to increase the bioavailability of griseofulvin, the drug was treated with small amounts of hydroxypropyl cellulose and formulated into capsules, see Fell et al, J. Pharm. Pharmac., 30, 479-482 (1978). While the formulation produced by this treatment increases the rate and extent of availability of micronized griseofulvin, the authors reported that the treated formulation does not always lead to complete absorption from the upper intestine as was reported for the Riegelman solid disperse system with polyethylene glycol 6000.

This invention provides compositions of poorly soluble or water insoluble drugs or relatively soluble drugs which have a tendency to agglomerate or crystallise in storage or after formulation into pharmaceutical dosage forms, which compositions provide higher dissolution rates in vitro and increased bioavailability of said drugs in vivo. The composition of this invention comprises a mixture or solution of the drug with a non-toxic, pharmacologically acceptable water soluble polymer wherein said mixture or solution has been treated with a minor amount of a wetting agent selected from anionic and cationic surfactants. The term mixture means the product of a melt mix or that of a dried solution.

Examples of suitable polymers are those selected from at least one of polyvinylpyrrolidone, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, block copolymers of ethylene oxide and propylene oxide, and polyethylene glycol. Suitable surfactants include those of the anionic variety such as sodium lauryl sulfate, sodium laurate, sodium stearate, potassium stearate, sodium oleate or dioctylsodium sulphosuccinate, and those of the cationic variety such as benzalkonium chloride, bis-2-hydroxyethyl oleyl amine or the like.

A further aspect of this invention provides a method for preparing compositions of this invention. The method includes the steps of:

(a) Forming a solution or melt mixture of a drug with a non-toxic, pharmacologically acceptable water-soluble polymer;

(b) drying the drug-polymer solution or solidifying the melt-mixture;

(c) mixing the product of step (b) with a surface wetting amount of wetting agent solution wherein said agent is selected from anionic and cationic surfactants;

and

(d) drying the mixture of step (c).

The method for preparing these compositions is also useful as a method for preparing ultramicrocrystalline griseofulvin.

While the invention is illustrated with poorly soluble or water insoluble drugs, and particularly griseofulvin, it will become apparent to those skilled in the art that the compositions and method of this invention are also suitable for other drugs which while relatively soluble have a tendency to agglomerate or crystallize in storage, or after formulation into pharmaceutical dosage forms.

This invention relates to compositions of a drug with a water soluble polymer which has been treated with a wetting sufficient amount of a wetting agent selected from anionic and cationic surfactants. In preferred embodiments the composition is a solid, usually a powder, which is then compounded into suitable solid dosage forms for oral administration.

Griseofulvin is a known antibiotic which has been found useful in the treatment of certain fungus diseases of plants, man and animals. Griseofulvin as discussed in the background of this invention is also known as a poorly soluble or water insoluble drug, which in vivo provides a low order of bioavailability when administered orally. Thus the composition of the instant invention is particularly useful for griseofulvin and drugs of a similar nature such as certain steroids and antibiotics which due to their low aqueous solubility and/or high melting point are poorly absorbed. Illustrative of such drugs are medrogestone; progesterone; estradiol; 10, 11-dihydro-5H-dibenzo[a,d] cycloheptene-5-carboxamide; 5H-dibenzo [a,d] cycloheptene-5-carboxamide and the like. The compositions of this invention, as will soon be appreciated, further permit the formulation of solid dosage forms which may contain high concentrations of the particular drug, such as griseofulvin, with no concomitant loss of bioavailability usually associated with such high concentrations. These compositions thus allow the preparation of elegant solid dosage forms. The compositions of this invention are also resistant to agglomeration of the drug particles or the tendency of the drug in storage to produce undesirable crystal formation which adversely affects bioavailability of the drug.

Polymers useful in this invention include water soluble polymers which are non-toxic and pharmacologically acceptable, particularly for oral administration. Illustrative of polymers, found suitable in this invention include polyvinylpyrrolidone, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, block co-polymers of ethylene oxide and propylene oxide, and polyethylene glycol.

Generally these polymers are commercially available over a broad range of average molecular weights. For example, polyvinylpyrrolidone (PVP) is a well known product produced commercially as a series of products having mean molecular weights ranging from about 10,000 to 700,000. Prepared by Reppe's process: 1,4-butanediol obtained in the Reppe butadiene synthesis is dehydrogenated over copper at 200° forming γ- butyrolactone; reaction with ammonia yields pyrrolidone. Subsequent treatment with acetylene gives the vinyl pyrrolidone monomer. Polymerization is carried out by heating in the presence of H_2O_2 and NH_3. DeBell et al., German Plastics Practice (Springfield, 1946); Hecht, Weese, Munch. Med. Wochenschr. 1943, 11; Weese, Naturforschung & Medizin 62, 224 (Wiesbaden 1948), and the corresp vol. of FIAT Review of German Science. Monographs: General Aniline and Film Corp., PVP (New York, 1951); W. Reppe, Polyvinylpyrrolidon (Monographie zu "Angewandte Chemie" no. 66, Weinheim/Bergstr., 1954). Generally available commercial grades have average molecular weights in the range of 10,000 to 360,000, for example, General Aniline and Film Corporation (GAF) markets at least four viscosity grades available as K-15, K-30, K-60, and K-90 which have average molecular weights of about 10,000, 40,000, 160,000 and 360,000, respectively. The K-values are derived from viscosity measurements and calculated according to Fikentscher's formula (Kline, G.M., Modern Plastics 137 No. 1945). Similar commercial products are available from BASF-Wyandotte.

Selection of a particular polymer with its characteristic molecular weight will in part depend on its ability to form suitable dosage forms with the particular drug. Thus, in preparing solid dosages, whether in powder, tablet or capsule units, the composition of this invention should be readily grindable or pulverizable, or in the form of free-flowing powders. A second consideration in the selection of a particular polymer derives from the limitations inherent in the use of specific equipment with polymers of increasingly higher viscosity.

For example in forming the drug-polymer solution or mixture, complete dissolution or mixing could be inhibited utilizing blenders, mixer or the like, which are inadequate by reason of low shear or proper baffles to form a uniform and homogeneous drug-polymer solution or mixture. Depending on the process employed for forming the drug-polymer mixture, another consideration in the selection of a particular polymer is that the polymer be mutually soluble in solvents for the particular drug.

The wetting agents found most suitable for the present invention are those selected from anionic or cationic surfactants. In addition, to those cited in the summary of this disclosure, other suitable surfactants of the anionic variety are illustrated by sodium stearate, potassium stearate, sodium oleate and the like.

The compositions of this invention are prepared in a step by step process.

In the first step, a mixture or solution of the drug with the water soluble polymer is formed. The mixture can be formed in a solvent or solvent mixture which is a mutual solvent for both the drug and the polymer. Alternatively, the drug-polymer, solvent mixture can, at this stage, be coated onto lactose. Where the drug and the polymer are not subject to degradation at elevated temperatures, the drug-polymer mixture may also be formed by melt mixing. Any volatile solvent in which the drug is soluble is suitable for forming the drug-polymer mixture. For griseofulvin, suitable solvents would include methylene chloride, methylene chloride-ethanol, chloroform, acetone, methyl ethyl ketone and combinations thereof. The most suitable polymer for forming the melt mixture with a drug such as griseofulvin is hydroxypropyl cellulose.

After the drug-polymer mixture or solution has been formed in a solvent it is dried by spray-drying, flash evaporation or air drying. Commercially, spray-drying is most practical since the dried mixture is already in powder form. In the case of the melt mixture drying the drug-polymer mixture is defined as cooling. The melt-mix product is then ground or milled into powder form in preparation for the next step; grinding or milling may also be necessary for dried solvent formed mixtures.

The powdered drug-polymer mixture is then treated with a wetting sufficient amount of a primarily aqueous wetting solution containing a wetting agent selected from anionic and cationic surfactants. This wetting treatment is

accomplished by forming a slurry, wet granulation or paste mixture of the powdered drug-polymer with the wetting solution. The wetting solution treatment can be achieved with small incremental additions of the wetting solution or a larger single-shot treatment. The wetting solution treatment apparently fulfills two roles: crystallization of any amorphous regions into ultramicrosize crystals, and the breakup of clusters of such crystals so that they disperse spontaneously when exposed to water. Also, the role of the primarily aqueous solution for the wetting agent treatment is to distribute the wetting agent to surfaces of the drug, whether or not the drug is amorphous or crystalline.

When the employment of more than one polymer is desired, separate drug-polymer mixtures for each polymer are usually prepared which are then initimately blended with each either in dry form prior to or after the wetting solution treatment.

The treated mixture is then dried as earlier described and, if necessary, it is milled, screened or ground prior to formulating into suitable dosage forms with pharmaceutically acceptable excipients.

It will be again appreciated by those skilled in the art that while the invention is illustrated with particularly water insoluble drugs, the composition and method of this invention is also applicable to more soluble drugs in need of enhanced bioavailability. In such instances a broader range of solvents and polymers including the natural gums may be employed to form the drug-polymer mixture.

The concentrations of drug found useful in the drug-polymer mixture of this invention range from the lowest therapeutically effective amount of the drug up to about 90 to 95% of the drug. Thus, in griseofulvin-polymer mixtures, the concentration of griseofulvin ranges from about 0.1% by weight to about 90-95% by weight. In order to form pharmaceutically elegant dosage forms for high dose drugs, the concentration of the drug should be at least 50% by weight of the drug-polymer mixture. In especially preferred embodiments the concentration of drug in the drug polymer mixture will range from about 50% to about 80% by weight.

The required concentration for the wetting agent (or surfactant) in the primarily aqueous wetting solution is a wetting sufficient amount. This amount further depends on whether incremental or single-shot wetting treatments are employed and on whether a slurry or paste treatment is contemplated. Generally, small incremental treatments will require less wetting agent than a larger single shot treatment and a paste treatment will require more wetting agent than a slurry. In any case, it has been found that satisfactory results are obtained when the amount of wetting agent comprises from about 0.025% to about 2.0% by weight of the dried drug polymer mixture and preferrably from about 0.1% or 0.2% to about 1.0% by weight. While higher concentrations of the wetting agent may be satisfactorily employed, no additional advantages in terms of dissolution and/or bioavailability are obtained. It has also been found that when a griseofulvin-polymer, melt mixture has been wetted and crystallized from an aqueous sorbitol solution, enhanced dissolution rates was obtained, however the rate of dissolution was still less that those mixtures treated with a wetting agent.

The invention is further illustrated by the following examples.

Example 1

The rate of dissolution of the powdered materials was determined by one of three methods. All three methods gave equivalent results and only the results of method 1 outlined below are used herein unless otherwised noted.

Method 1) A sample containing 20 mg of griseofulvin was dissolved into 1 liter of a 0.02% polysorbate 80 aqueous solution at 37° C. The solution was monitored by a flow cell in a spectrophotometer set at 295 nm.

Method 2) A sample containing 500 mg griseofulvin was dissolved in 10 liters of 0.15% sodium lauryl sulfate in water at 37° C.

Method 3) A sample containing 125 mg griseofulvin was dissolved in 24 liters of water at 37° C.

For examples 2-5 the wetting agent solution employed was as follows: 2.5g of sodium lauryl sulfate (SLS) were dissolved into 500 ml of a mixture of 100 ml of water and 400 ml of ethyl alcohol or 0.25 g of sodium lauryl sulfate were dissolved into 50 ml of a mixture of 10 ml of water and 40 ml of ethyl alcohol.

Example 2

This example describes the preparation of ultramicrocrystalline griseofulvin. The method consists of flash evaporation of a solution containing 10 g of griseofulvin and 10 g of polyvinylpyrrolidone (POVIDONE® K-30, U.S.P.-from GAF Corp.) dissolved in 200 ml of methylene chloride. The evaporation was done on a rotating evaporator at 35 - 45° C in a closed system (Vacuum). About 4 - 5 ml of the solution to be evaporated was placed in a 100 ml round bottom flask, then placed on the evaporator. Upon evaporation of solvent, the material was deposited onto the wall of the flask. The dried material was found to be amorphous by X-ray diffraction. Next, this amorphous material was treated with the SLS solution. To 2 g of powder, 0.125 ml of the solution was added with constant mixing and the solvent was allowed to dry. This was repeated six more times until a total of 0.875 ml of solution had been added. Microscopic observation and dissolution data showed that ultramicrocrystalline griseofulvin was formed by this method and has a much faster dissolution rate into water at 37° C, than microsized griseofulvin or untreated amorphous material

Table 1 - Dissolution profile of griseofulvin into water at 37° C. The dissolved griseofulvin, unless otherwise specified, is expressed in mg/liter over an elapsed time period in minutes.

1- Flash evaporated griseofulvin: PVP (50% griseofulvin) treated with SLS solution.

2- Flash evaporated griseofulvin: PVP (50% griseofulvin)

3- Microsized griseofulvin

Sample	1 min.	2 min.	3 min.	5 min.	10 min.	14 min.
1	11.2	11.7	11.9	12.0	12.2	12.5
2	2.5	3.8	4.8	6.5	8.7	9.8
3	1.6	2.7	3.4	4.7	7.0	8.2

Example 3

Table 1 - This example describes the preparation of ultramicrocrystalline griseofulvin by coating a solution of griseofulvin and polyvinylpyrrolidone onto lactose then treating the powder with a solution of sodium lauryl sulfate.

A solution was prepared by dissolving 1 g of griseofulvin and 1 g of polyvinylpyrrolidone into 8 ml of methylene chloride. All this solution was coated successively in 1 ml portions onto 2 g of lactose and allowed to dry. The material formed by this method was crystalline by X-ray diffraction. Next 1 ml of the SLS solution was added to the 4 g of powder and allowed to dry. Microscopic observation and dissolution data showed that the griseofulvin formed by this method was ultramicrocrystalline and had a much faster dissolution rate into water at 37° C, than microsized griseofulvin.

Table 2 -

1- griseofulvin: PVP (50:50) coated onto lactose and treated with SLS solution.

2- griseofulvin: PVP (50:50) coated onto lactose.

3- Microsized griseofulvin

Sample	1 min.	2 min.	3 min.	5 min.	10 min.	14 min.
1	10.8	11.6	11.8	11.9	12.0	12.0
2	7.0	8.7	9.7	10.5	11.5	11.5
3	1.6	2.7	3.4	4.7	7.0	8.2

Example 4

This example describes the preparation of ultramicrocrystalline griseofulvin by spray drying a solution of griseofulvin and polyvinylpyrrolidone then treating the powder with a solution of sodium lauryl sulfate. A solution of 50 g of griseofulvin and 50 g of polyvinylpyrrolidone dissolved in 2 liters of methylene chloride was spray dried at room temperature. A mixture of 1 ml of the SLS solution and 2 g of the powder was dried. Microscopic observation and dissolution data showed the griseofulvin formed by this method to be ultramicrocrystalline and has a much faster dissolution rate into water at 37° C than microsized griseofulvin.

Table 3

1- Spray dried griseofulvin: PVP (1:1) treated with SLS solution.
2- Spray dried griseofulvin: PVP (1:1)
3- Microsized griseofulvin

Sample	1 min.	2 min.	3 min.	5 min.	10 min.	14 min.
1	10.5	10.7	10.8	11.0	11.0	11.0
2	3.2	4.4	5.6	8.1	9.9	10.4
3	1.6	2.7	3.4	4.7	7.0	8.2

Example 5

This example describes preparation of ultramicrocrystalline griseofulvin by spray drying a solution of griseofulvin and polyvinylpyrrolidone and then treating the powder with a solution of sodium lauryl sulfate. A solution containing 70 g of griseofulvin and 30 g of polyvinylpyrrolidone dissolved into 2 liters of methylene chloride was spray dried at room temperature. To 2 g of the powder, 3/4 ml of the SLS solution was added in six 0.125 ml increments and dried between additions. Microscopic observation and dissolution data showed that the griseofulvin formed by this method was ultramicrocrystalline and had a much faster dissolution rate into water at 37° C than microsized griseofulvin.

Table 4

1- Spray dried griseofulvin: PVP (70:30) treated with SLS solution.

2- Spray dried griseofulvin: PVP (70:30).

3- Microsized griseofulvin

4- Spray-dried griseofulvin: PVP treated with the non-ionic polysorbate 80. griseofulvin: PVP: non-ionic (69.7:29.7:0.5)

5- Spray dried griseofulvin: PVP treated with the non-ionic block copolymer of ethylene oxide and propylene oxide (Pluronic®F77) griseofulvin: PVP: non-ionic (69.7:29.7:0.5)

6- Spray dried griseofulvin: PVP treated with the non-ionic isooctyl phenoxy polyethoxy ethanol. griseofulvin PVP: non-ionic (69.7:29.7: 0.5)

Sample	1-min.	2 min.	3 min.	5 min.	10 min.	14 min.	15 min.
1	10.0	10.9	11.5	12.0	12.5	12.7	—
2	2.5	3.9	4.9	6.5	9.0	10.4	—
3	1.6	2.7	3.4	4.7	7.0	8.2	—
4	1.9	3.5	4.6	6.3	8.6	—	9.7
5	1.8	3.0	4.0	5.8	8.1	—	9.3
6	1.9	3.1	4.3	6.0	8.6	—	9.7

Table 5 - Dissolution Profile

1- Spray dried griseofulvin: PVP (70:30) treated with SLS

2- Dorsey Laboratories' Gris-Peg (Trademark) for griseofulvin composition in PEG 6000.

3- Schering Laboratories' Fulvicin P/G (Trademark) for griseofulvin composition in PEG 6000.

4- Microsized griseofulvin.

Sample	1 min.	2 min.	3 min.	5 min.	10 min.	14 min.
1	10.0	10.9	11.5	12.0	12.5	12.7
2	6.9	8.7	9.7	10.4	11.3	—
3	6.0	7.0	7.3	7.7	8.0	—
4	1.6	2.7	3.4	4.7	7.0	8.2

Example 6

In the samples evaluated in Tables 6-8, the following further describes their preparation.

MATERIALS & METHODS

Two grades of hydroxypropyl cellulose were used, Klucel®EF and Klucel® LF (Hercules), the former preferred for its lower viscosity. Coarse griseofulvin, spray dried lactose, sorbitol, and sodium lauryl sulfate were the other ingredients. The solvents were methylene chloride and absolute ethanol, U.S.P. grade.

Crystallinity of griseofulvin preparations were judged by visual microscopic observation under crossed polarizers, or by x-ray diffraction assay.

Preparation of a Melt Mixture

A glass melting tube immersed in a hot oil bath was used to melt together various amounts of griseofulvin and Klucel. After complete melting and mixing, the liquid mixture was rapidly chilled under a cold water tap, while rotating the tube horizontally so as to distribute the liquid over the inside walls. After solidification, the tube was further cooled in a dry ice bath, which fractured the product and allowed its removal from the glass tube. The chunky product was ground to a powder in a micromill.

Crystallization with a Sorbitol Solution

Typically, an amount of powdered melt mixture was intimately mixed with an equal weight of an aqueous solution containing, by weight, about 22% sorbitol and 13% ethanol. This was vigorously mixed and worked with a spatula, until the doughy mixture acquired the consistency of a smooth cream or paste. The paste was allowed to dry, and the dry chunky product was ground in a mortar.

Spray Dried Mixtures

Solution for spray drying were prepared by dissolving griseofulvin and Klucel in a mixture of methylene chloride and ethanol. An Anhydro Laboratory Spray Dryer No. 3 was used, and the solution was spray dried at room temperature.

Crystallization with a Sodium Lauryl Sulfate Solution

Typically, a weight of spray dried powder (whether amorphous or crystalline) was intimately mixed with about 0.9 weight of a 1.5% aqueous solution of sodium lauryl sulfate. The solution could also contain ethanol and sorbitol or lactose, but this was found to be unnecessary. The doughy mixture was vigorously mixed and worked with a spatula, until it became a smooth paste. Then, about 0.25 weight of lactose was added, and mixed until again smooth. The paste was spread and dried at around 85° C. The elevated temperature coagulated the wet paste into granules, which could be stirred and mixed at times during drying, to diminish caking. The dry product was milled and passed through a 60 or 80 mesh screen. The product contained about 1% sodium lauryl sulfate.

Treatment of Spray Dried Mixtures with Sodium Lauryl Sulfate Solution, Without Pasting

About 2.0 g of spray dried griseofulvin-Klucel®mixture was placed in a mortar, then treated successively with six 0.125 ml portions of a wetting solution, allowing enough drying between portions to prevent the powder from becoming pasty. The wetting solution contained 5 mg/ml sodium lauryl sulfate in a mixture of 4 parts ethanol - 1 part water, by volume. The final granular powder contained about 0.2% sodium lauryl sulfate.

Scale-up Attempts of Paste Treatment

Crystallization of spray dried powders with sodium lauryl sulfate solution on a 1 kg scale were achieved in a Hobart mixer, equipped with a small bowl and a pastry blade. Lactose was added to the paste, then the mixture was spread on trays and dried at 85° C. The chunky, partially caked product was milled and screened.

Spray Dried Mixtures of Griseofulvin & Hydroxypropyl cellulose (Klucel)®

Composition of Solution			
Solids Content (g/l of solvent)	Griseofulvin Content (% of Solids)	Solvent Volume Ratio ($MeCl_2$/EtOH)	Crystallinity of Product
100	50	7/1	Mostly amorphous
50	75	9/1	Amorphous
167	75	8.6/1	Crystalline
200	80	7/1	Crystalline

Table 6 - Dissolution profile.

1- Melt mixture of griseofulvin (75%)-Klucel®(25%),crystallized with a sorbitol solution

2- Micronized griseofulvin

3- Melt mixture of griseofulvin (83%)-Klucel®(17%),amorphous.

Sample	1 min.	2 min.	3 min.	5 min.	10 min.	15 min.	20 min.
1	4.1	8.0	9.2	10.8	12.6	13.4	13.7
2	1.5	2.7	3.4	4.7	7.0	8.4	9.2
3	0.5	1.0	1.3	2.0	3.2	4.2	5.0

Table 7

1- Spray dried griseofulvin (75%)-Klucel®(25%) mixture, amorphous.

2- Spray dried griseofulvin (50%)-Klucel®(50%) mixture, mostly amorphous.

3- Micronized griseofulvin.

4-Spray dried griseofulvin (80%)-Klucel ®(20%) mixture crystalline.

Sample	1 min.	2 min.	3 min.	5 min.	10 min.	15 min.	20 min.
1	2.0	3.6	4.7	6.5	9.8	11.4	12.8
2	2.0	3.6	4.7	6.5	9.2	10.5	11.8
3	1.5	2.7	3.4	4.7	7.0	8.4	9.2
4	0.8	1.5	2.0	2.8	4.7	5.8	6.5

Table 8

1- Spray dried mixture of griseofulvin: PVP (70:30), treated with SLS solution.

2- Spray dried mixture of griseofulvin: Klucel®(75:25), crystallized with sodium lauryl sulfate solution.

3- Micronized griseofulvin

Sample	1 min.	2 min.	3 min.	5 min.	10 min.	15 min.	20 min.
1	6.2	11.1	11.5	12.0	12.5	12.7	12.8
2	6.2	10.2	11.0	11.6	12.1	12.2	12.3
3	1.5	2.7	3.4	4.7	7.0	8.4	9.2

Example 7

This example describes preparation of ultramicrocrystalline griseofulvin by spray drying a solution of griseofulvin and hydroxypropyl methyl cellulose and then treating the powder with a solution of sodium lauryl sulfate. A solution containing 40 g of hydroxypropyl methylcellulose 80 g of griseofulvin and 200 ml of Methanol dissolved into 2 liters of methylene chloride was spray dried at R.T. The dried material was found to be amorphous by x-ray diffraction. To 4 g of the powder, 4 ml of a solution containing 1.5 g sodium

lauryl sulfate dissolved into 100 ml of H_2O was mixed in, and then dried. Microscopic observation and dissolution data shows that ultramicrocrystalline griseofulvin was formed by this method and has a much faster dissolution rate into water at 37° C, than microsized griseofulvin or untreated amorphous material.

Example 8

This example describes preparation of ultramicrocrystalline griseofulvin by spray drying a solution of griseofulvin and methylcellulose and then treating the powder with a solution of sodium lauryl sulfate. A solution containing 40 g of methylcellulose (15 cps) and 120 g of griseofulvin, and 200 ml of methanol dissolved into 2 liters of methylene chloride was spray dried at R.T. The dried material was found to be partly amorphous and partly crystalline by x-ray diffraction. To 4 g of the powder, 4 ml of a 1.5% sodium lauryl sulfate solution was added and mixed in. The mixture then was dried. Microscopic observation and dissolution data shows that ultramicrocrystalline griseofulvin was formed by this method, and it has a much faster dissolution rate than microsized griseofulvin or untreated material.

Example 9

This example describes preparation of ultramicrocrystalline griseofulvin by spray drying a solution of griseofulvin and poly (oxypropylene) poly (oxyethylene) block copolymer (Pluronic®F77 BASF Wyandotte Corp.) and then treating the powder with a solution of sodium lauryl sulfate. A solution containing 100 g of the block copolymer and 100 g griseofulvin dissolved into 2 liters of methylene chloride was spray dried at RT, to 4 g of the powder, 2 ml of a 1.5% sodium lauryl sulfate was added, mixed and then dried. Microscopic observation and dissolution data shows that ultramicrocrystalline griseofulvin was formed by this method, and it has a faster dissolution rate than microsized griseofulvin or untreated material.

Example 10

This example describes preparation of ultramicrocrystalline griseofulvin by spray drying a solution of griseofulvin and polyethylene glycol and then treating the powder with a solution of sodium lauryl sulfate. A solution containing 100 g of griseofulvin and 100 g of polyethylene glycol 6000 dissolved into methylene chloride was spray dried. To 4 g of the powder, 2 ml of a 1.5% sodium lauryl sulfate solution was added, mixed and dried. Microscopic observation and dissolution data shows that ultramicrocrystalline griseofulvin was formed by this method, and it has a much faster dissolution rate than microsized griseofulvin or untreated material.

Example 11

This example describes preparation of ultramicrocrystalline griseofulvin by spray drying a solution containing griseofulvin and hydroxypropyl methylcellulose and then treating the powder with a solution of sodium lauryl sulfate. A solution containing 40 g of hydroxypropyl methylcellulose, 160 g of griseofulvin and 100 ml of ethanol dissolved into 2 liters of methylene chloride was spray dried. To 2 g of powder, 0.125 ml of sodium lauryl sulfate wetting solution (see above example No. 7) was added with constant mixing and the solvent was allowed to dry. This was repeated five more times until a total of 0.750 ml of solution had been added. Microscopic observation and dissolution data shows that ultramicrocrystalline griseofulvin was formed by this method and it has a much faster dissolution rate than microsized griseofulvin or untreated material.

Example 12

This example describes preparation of ultramicrocrystalline griseofulvin by spray drying a solution of griseofulvin and polyvinylpyrrolidone and then treating the powder with a solution of benzalkonium chloride. A solution of 70 g of griseofulvin and 30 g of polyvinylpyrrolidone dissolved into 2 liters of methylene chloride was spray dried at RT. To 4 g of the powder, 2 ml of a 1% aqueous solution of benzalkonium chloride was added, mixed and then dried. Microscopic observation and dissolution data shows that ultramicrocrystalline griseofulvin was formed by this method, and it has a much faster dissolution

rate than microsized griseofulvin or untreated material.

Example 13

This example describes preparation of ultramicrocrystalline griseofulvin by spray drying a solution of griseofulvin and polyvinylpyrrolidone and then treating the powder with a solution of sodium laurate. A solution of 70 g of griseofulvin and 30 g of polyvinylpyrrolidone dissolved into 2 liters of methylene chloride was spray dried at RT. To 4 g of the powder, 2 ml of a 2% aqueous solution of sodium laurate was added, mixed and then dried. Microscopic observation and dissolution data shows that ultramicrocrystalline griseofulvin was formed by this method, and it has a much faster dissolution rate than microsized griseofulvin or untreated material.

Example 14

This example describes preparation of ultramicrocrystalline griseofulvin by spray drying a solution of griseofulvin and polyvinylpyrrolidone and then treating the powder with a solution of dioctyl sodium sulfosuccinate. A solution of 70 g of griseofulvin and 30 g of polyvinylpyrrolidone dissolved into 2 liters of methylene chloride was spray dried at RT. To 4 g of the powder, 2 ml of a 1% aqueous solution of dioctyl sodium sulfosuccinate was added, mixed and then dried. Microscopic observation and dissolution data shows that ultramicrocrystalline griseofulvin was formed by this method, and it has a much faster dissolution rate than microsized griseofulvin or untreated material.

Example 15

This example describes preparation of ultramicrocrystalline griseofulvin by spray drying a solution of griseofulvin and polyvinylpyrrolidone and then treating the powder with a solution of bis(2-hydroxyethyl)oleylamine. A solution of 70 g of griseofulvin and 30 g of polyvinylpyrrolidone dissolved into 2 liters of methylene chloride was spray dried at RT. To 4 g of the powder, 2 ml of a 2%aqueous solution of bis(2-hydroxyethyl)oleylamine was added, mixed and then dried. Microscopic observation and dissolution data shows that ultramicrocrystalline griseofulvin was formed by this method, and it has a much faster dissolution rate than microsized griseofulvin or untreated material.

Table 9

The results of dissolution studies on the samples prepared by Examples 7-15 are listed below. The unit of expression for this Table is per cent of saturation achieved in time expressed in minutes.

Polymer	Wetting Agent	wt.% Polymer	Wetting Agent	Griseofulvin	Percent of Saturation-time Min. 1	2	3	4	5	10	15	20	25
None-Griseofulvin Microsized	None	None	None	100%	14.8	22.3	30.3	36.8	42.6	64.5	76.1	83.1	86.5
PVP	SLS	49.9	0.2	49.9	92.9	99.2	100.6	101.3	101.9				
PVP	SLS	29.9	0.2	69.9	91.6	97.0	98.8	99.4	99.6	100.0			
PVP	SLS	9.9	0.2	89.9	60.7	70.0	89.0	83.9	85.8	91.6	93.5	94.8	95.6
PVP	BAC	29.8	0.5	69.7	75.7	87.2	92.6	95.3	97.0	99.3	100		
PVP	DSS	29.8	0.5	69.7	86.5	92.9	95.5	96.8	97.4	98.3	99.8		
PVP	SL	29.7	1.0	69.3	53.5	65.2	72.3	77.4	81.9	90.3	94.8		
PVP	BHOA	29.7	1.0	69.3	74.2	83.9	88.6	91.6	93.2	97.4	100.00	100.6	
HPC	SLS	24.9	0.2	74.9	85.4	93.2	96.7	98.3	99.3	101.9			
HPC	SLS	19.9	0.2	79.9	61.9	71.6	77.4	81.5	84.5	94.2	99.4	101.9	109.0
HPMC	SLS	32.8	1.5	65.8	36.8	49.0	57.4	69.8	67.7	88.4	101.3	108.4	112.9
PEG	SLS	49.6	0.7	99.6	71.2	83.2	89.6	92.9	94.5	98.3	99.4	99.6	
POE/POP	SLS	44.6	0.7	49.6	43.2	56.7	63.8	68.6	72.3	81.3	85.4	87.7	89.0

*Saturation 11.6 mg liter

PVP= Polyvinylpyrrolidone

SLS= Sodium Lauryl Sulphate

HPC= Hydroxypropylcellulose

PEG= Polyethylene Glycol

HPMC= Hydroxypropyl Methyl Cellulose

POE/POP=Polyoxyethylene Polyoxypropylene Copolymer

BHOA= Bis(2-hydroxyethyl)oleylamine

SL= Sodium Laurate

BAC= Benzalkonium Chloride

DSS= Dioctyl Sodium Sulfosuccinate

Example 16

The relative bioavailability of the composition of this invention with two different polymer mixtures and that of one marketed ultramicrosize griseofulvin dosage form was studied in humans.

The urinary excretion of the major griseofulvin metabolite 6-Desmethyl griseofulvin (6-DMG) was determined for all three dosage forms following the administration of 250 mg of griseofulvin (in the form of 125mg tablets) to 15 healthy adult volunteers divided into three groups using a crossover experimental design. The total tablet weight for each of the 125 mg dosages was 350 mg. The compositions of the invention were represented by spray dried griseofulvin mixtures with either polyvinylpyrrolidone or hydroxypropyl cellulose both treated with SLS. The marketed product evaluated was Schering's Fulvicin® P/G which is perceived as providing maximum bioavailability or absorption following oral administration.

The results indicated that there were no statistically significant differences between the 3 dosage forms evaluated.

The cumulative mean for all groups expressed in mg of either free or total 6-DMG found in the urine for each of the three dosages was as follows:

	Gris-PVP		Gris-hydroxypropyl cellulose		Marketed Product	
	Free	Total	Free	Total	Free	Total
0-24 hours	48:6	75.8	50.3	81.1	48.9	76.7
24-48 hours	19.1	30.0	20.7	33.3	19.5	37.1
0-48 hours	68.7	105.8	71.0	114.4	68.4	113.8

In a second bioavailability study conducted with 4 healthy adult volunteers, dosage forms containing 500 mg of micronized griseofulvin were administered in the form of a single tablet or 2 capsules each containing 250 mg of micronized griseofulvin. Since griseofulvin is not a dose dependent drug, twice the amount of the 6-DMG metabolite should be excreted over that of a 250 mg dosage of griseofulvin.

The cumulative mean was as follows:

	500mg Griseofulvin Tablet		500mg Griseofulvin as 2x250mg capsules	
	Free	Total	Free	Total
0-24 hours	34.4	35.5	38.0	54.7
24-48 hours	63.5	104.2	64.4	102.8
0-48 hours	97.9	157.9	102.4	157.5

Example 17

Typical direct compression tablet formulations may be prepared as follows for 125 mg dosage forms having a final tablet weight of 350 mg.

A. 1. Griseofulvin at 59.5% in mixture with hydroxypropyl cellulose, SLS treated	210.0 g
2. Microcrystalline Cellulose	87.0 g
3. Lactose, Edible	32.0 g
4. Sodium Starch Glycolate	17.5 g
5. Magnesium Stearate U.S.P.	3.5 g
Theoretical Tablet Weight	350 mg.
B.1. Griseofulvin at 67.5% in PVP mixture treated with SLS	185.0 g
2. Microcrystalline Cellulose	87.0 g
3. Lactose, Edible	67.0 g
4. Sodium Starch Glycolate	17.5 g
5. Magnesium Stearate	3.5 g
Theoretical Tablet Weight	350 g

In both A and B, ingredients 1-4 were blended together until uniform, passed through a screen, blended with ingredient 5 and compressed at the correct tablet weight.

The dissolution profile for the compressed tablets demonstrated further that there was no significant difference in dissolution for the formulated tablet as compared with the unformulated powdered material.

CLAIMS

1. A pharmaceutical composition comprising a mixture of a drug and a non-toxic pharmacologically acceptable, water soluble polymer; the drug being poorly soluble or water-insoluble or relatively soluble and having a tendency to agglomerate or crystallise in storage or after formulation into pharmaceutical dosage forms; said mixture having been treated with a minor amount of a wetting agent selected from anionic and cationic surfactants.

2. A composition as claimed in Claim 1 wherein the polymer is selected from at least one of polyvinylpyrrolidone, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, block co-polymers of ethylene oxide and propylene oxide, and polyethylene glycol.

3. A composition as claimed in Claim 1 or Claim 2 wherein the wetting agent is an anionic surfactant selected from sodium lauryl sulfate, sodium laurate, dioctylsodium sulfosuccinate, sodium stearate, potassium stearate and sodium oleate, or a cationic surfactant selected from benzalkonium chloride and bis-2-hydroxyethyl oleyl amine.

4. A composition as claimed in any one of Claims 1 to 3 wherein the concentration of the drug in the drug-polymer mixture is from about 0.1% to about 95% by weight and the concentration of the polymer in the drug-polymer mixture is from about 5% to about 99.9% by weight.

5. A composition as claimed in any one of Claims 1 to 3 wherein the concentration of the drug in the drug-polymer mixture is from about 50% to about 90% by weight and the concentration of the polymer in the

drug-polymer mixture is from about 10% to about 50% by weight.

6. A composition as claimed in any one of Claims 1 to 3 wherein the concentration of the drug in the drug-polymer mixture is about 50% to about 80% by weight and the concentration of the polymer in the drug-polymer mixture is from about 20% to about 50% by weight.

7. A composition as claimed in any one of Claims 1 to 6 wherein the concentration of the wetting agent is from about 0.025% to about 2.0% by weight of the drug-polymer mixture.

8. A composition as claimed in any one of Claims 1 to 6 wherein the concentration of the wetting agent is from about 0.2% to about 1.0% by weight of the drug-polymer mixture.

9. A composition as claimed in any one of Claims 1 to 8 wherein the drug is griseofulvin.

10. A pharmaceutical composition in solid form comprising (i) a mixture comprising about 0.1% to about 95% by weight of griseofulvin and from about 5% to about 99.9% by weight of a polymer selected from polyvinyl-pyrrolidone, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, methyl cellulose, block co-polymers of ethylene oxide and propylene oxide, and polyethylene glycol; and (ii) an anionic surfactant wetting agent in an amount from about 0.025% to about 2.0% by weight of griseofulvin-polymer mixture which was added to the griseofulvin-polymer mixture by a wet treatment.

11. A composition as claimed in Claim 10 wherein the concentration of the griseofulvin in the griseofulvin-polymer mixture is from about 50% to about 80% by weight; the polymer is selected from polyvinyl-pyrrolidone and hydroxypropyl cellulose and the concentration in the griseofulvin-polymer mixture is from about 20% to about 50% by weight; and the anionic surfactant is sodium lauryl sulfate, sodium sulfate or dioctylsodium sulfosuccinate in an amount from about 0.2 to about 1.0% by weight of the griseofulvin-polymer mixture.

12. A compressed pharmaceutical tablet comprising a pharmaceutically acceptable excipient and a composition as claimed in any one of Claims 1 to 11 wherein the drug is in the form of ultramicrocrystals.

13. A method for preparing a pharmaceutical composition as claimed in any one of Claims 1 to 11, which comprises:
    (a) forming a solution or melt-mixture of the drug with the polymer;
    (b) drying the drug-polymer solution or solidifying the melt mixture,
    (c) mixing the product of step (b) with a wetting agent solution, and
    (d) drying the mixture of step (c).

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CLAIMS FOR AUSTRIA

1. A process for preparing a pharmaceutical composition comprising a poorly soluble or water-insoluble drug or a relatively soluble drug having a tendency to agglomerate or crystallise in storage or after formulation into pharmaceutical dosage forms, which process comprises the following steps:
   (a) forming a solution or melt-mixture of the drug with a pharmacologically acceptable water-soluble polymer;
   (b) drying the drug-polymer solution or solidifying the drug-polymer melt-mixture;
   (c) mixing the product of step (b) with a wetting agent solution wherein the wetting agent is selected from anionic and cationic surfactants, and
   (d) drying the mixture of step (c).

2. A process as claimed in Claim 1 wherein the polymer is selected from at least one of polyvinylpyrrolidone, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, block co-polymers of ethylene oxide and propylene oxide, and polyethylene glycol.

3. A process as claimed in Claim 1 or Claim 2 wherein the wetting agent is an anionic surfactant selected from sodium lauryl sulfate, sodium laurate, dioctylsodium sulfosuccinate, sodium stearate, potassium stearate and sodium oleate, or a cationic surfactant selected from benzalkonium chloride and bis-2-hydroxyethyl oleyl amine.

4. A process as claimed in any one of Claims 1 to 3 wherein the concentration of the drug in the drug-polymer mixture is from about 0.1% to about

95% by weight and the concentration of the polymer in the drug-polymer mixture is from about 5% to about 99.9% by weight.

5. A process as claimed in any one of Claims 1 to 3 wherein the concentration of the drug in the drug-polymer mixture is from about 50% to about 90% by weight and the concentration of the polymer in the drug-polymer mixture is from about 10% to about 50% by weight.

6. A process as claimed in any one of Claims 1 to 3 wherein the concentration of the drug in the drug-polymer mixture is about 50% to about 80% by weight and the concentration of the polymer in the drug-polymer mixture is from about 20% to about 50% by weight.

7. A process as claimed in any one of Claims 1 to 6 wherein the concentration of the wetting agent is from about 0.025% to about 2.0% by weight of the drug-polymer mixture.

8. A process as claimed in any one of Claims 1 to 6 wherein the concentration of the wetting agent is from about 0.2% to about 1.0% by weight of the drug-polymer mixture.

9. A process as claimed in any one of Claims 1 to 8 wherein the drug is griseofulvin.

10. A process as claimed in any one of Claims 1 to 12 comprising the further step of compressing a mixture of the composition and a pharmaceutically acceptable excipient to form tablets.

European Patent Office

EUROPEAN SEARCH REPORT

0012523
Application number
EP 79 30 2620

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
X	FR - A - 2 256 765 (BAYER) * Page 1, line 1- page 3, line 18; example 2; claims *	1-13
	FR - A - 2 204 425 (HOECHST) * Page 1, lines 23-36; page 2, lines 9-25; page 4, line 20 - page 5, line 27; claims 2-4 *	1-8, 12,13
	FR - A - 2 331 327 (SANDOZ) * Page 1, line 9 - page 2, line 12; page 2, line 26 - page 3, line 7; claims *	1,2,4-6,9-13
D	JOURNAL OF PHARMACEUTICAL SCIENCES, no. 55, 1966, pages 1323,1324 Washington, U.S.A. M. MAYERSOHN et al.: "New method of solid-state dispersion for increasing dissolution rates" * The whole article *	1,2,4-9
D	CA - A - 987 588 (RIEGELMAN) * Page 2, line 1 - page 3, line 5; page 4, line 8 - page 6, line 8; page 8, line 1 - page 9, line 2; page 17, lines 11-21; page 12, table I; example 1; claims 1-5 *	1,2,4-9
	FR - A - 2 285 855 (KOHJIN) * Page 1, line 30 - page 5, line 2; claims 1,3,13,15 *	1,2,4-8

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CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)

A 61 K 9/14
9/20

TECHNICAL FIELDS SEARCHED (Int.Cl. ³)

A 61 K 9/14
9/20

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons
&: member of the same patent family, corresponding document

X The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	04-03-1980	GERMINARIO

EPO Form 1503.1 06.78

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
P,X	DE - A - 2 822 882 (YAMANOUCHI PHARM.) * Page 5, lines 5-28; page 6, line 24 - page 10, line 27; examples 1-12,19; claims 1-10, 13,14 *	1-13	
A	GB - A - 1 055 854 (HOFFMANN LA ROCHE) * Page 1, line 75 - page 3, line 39 *	1,2,4-8	TECHNICAL FIELDS SEARCHED (Int. Cl. ³)
A	GB - A - 921 555 (DEREL) * Page 1, line 10 - page 2, line 37; claims 1-6 *	1-3	
D,A	US - A - 4 024 240 (TAKKAR) * Column 1, lines 12-42; column 5, lines 18-61; column 8, example 6 *	1-8	
D,A	US - A - 3 673 163 (WALKLING) * Column 1, lines 30-55; examples 1,2 *	1,2	